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Version: Version of Record

Link(s) to article on publisher's website:

<http://dx.doi.org/doi:10.21954/ou.ro.0000f7fa>

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HOMEOSTASIS AND ENERGY STORAGE  
IN MAN

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Submitted for the degree of Bachelor of Philosophy  
in the department of Biology in the Open University

Sept. 1986

Date of Submission: September 1986  
Date of Award: 15.10.86

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## ABSTRACT

Western man does not in general appear to operate homeostatic mechanisms to control his energy storage. Fragmentation makes it difficult to draw comprehensive conclusions from the literature research, a report of which is included, and the fact that much of the energy balance work is based on experimentation with other species raises questions of relevance. Individual human beings may vary with regard to biochemical type or may experience phase difference in a famine/feast rhythm. These theories and the involvement of brown adipose tissue are examined in some detail. An attempt to 'type' individuals by measurement of respiratory quotient failed. A pilot investigation into core temperature difference shows promise. The responses to three questionnaire forms are analysed. Two questionnaires reveal a high level of anxiety about body weight among young people. The third investigates calcium and vitamin D consumption and the possibility of linkage with famine/feast phase state. It is concluded that although recognition of 'type' or 'phase state' might well provide a short cut, ultimately individual experimentation with a variety of foods is likely to be necessary, if diet modification is to reduce weight without adverse complications.

ACKNOWLEDGMENTS

I am indebted to W.E.R. Pover, senior lecturer in biochemistry in the University of Birmingham, for his stimulating supervision from 1975 to 1979 and for the facilities offered by his department.

I also wish to thank

the students and staff of Dudley College of Education  
(1976)

the pupils of Lordswood Girls' School, Harborne  
(1976)

Mr L Harris and employees at Harris's Brush Works,  
Bromsgrove (1982)

Mr Jones and members of the personnel department of  
Mitchells and Butlers, Cape Hill (1982)

members of Lordswood Girls' and Foundry Road Primary  
teaching staffs (1982)

relations, friends and acquaintances

all of whom answered questions or submitted to measurement.

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## I SUMMARY

Western man does not in general appear to operate homeostatic mechanisms to control his energy storage.

A research into the literature revealed a wealth of observation, speculation and experimentation, the latter mainly with animals or in vitro, but fragmentation made it difficult to draw comprehensive conclusions, particularly where humans were concerned. Samples and conditions differed to such an extent that findings could not validly be compared.

It is here suggested firstly that individuals may vary with respect to their biochemical type, possibly across a spectrum, the extremes of which are 'fast oxidisers' and 'slow oxidisers' (Watson 1972) and this variation should be taken into account when weight adjustment measures are contemplated. The anxiety caused by overweight, on the one hand, and the psychiatric side effects of diet restriction, on the other, are also important.

An attempt was made to produce an accurate, portable means for inferring blood pH (Watson's most valued parameter) from Respiratory Quotient but incomplete knowledge of partition in solutions of carbonic acid threatened the accuracy of the inference. (see Note Seven)

Meanwhile a questionnaire (n = 186) revealed a high level of anxiety about body weight amongst young people and a second research amongst relevant literature suggested the implication of brown adipose tissue and also the famine/feast rhythm in energy storage control.

The variability of individuals is then re-examined in the light of related research and there is a switch of emphasis from 'individual types' to individuals at different phases of a basic rhythm, which civilisation has disturbed. Interest is centred round recognition of 'state' and a search for the 'trigger' which might initiate a change of phase, some attention being focused on the plasma calcium homeostatic

control system.

A further questionnaire made a preliminary attempt to seek out unusually heavy or unusually scanty consumption of calcium together with, more importantly, large or small intakes of Vitamin D. The sample ( $n = 95$ ) was too small for conclusions to be drawn and no clear pattern was suggested other than a possible sex linked involvement with Vitamin D consumption in young, slightly overweight individuals, which perhaps deserves further investigation.

A modest attempt ( $n = 31$ ) was made to bring one part of the first questionnaire up to date and this showed that unnecessary anxiety connected with weight still occurred amongst young females.

A pilot investigation aimed at identifying 'phase state' through measurement of core temperature showed some promise.

It is concluded that although recognition of 'type' or 'phase state' might well provide a short cut, ultimately individual experimentation with a variety of foods is likely to be necessary, if diet modification is to reduce weight without adverse complications.

## II INTRODUCTION

Man is, to quote Danforth (1981), 'a periodic eater and a constant metaboliser' and he must therefore carry an energy store. According to Bell, Emslie-Smith and Paterson (1980) the constant activity of the brain takes about one quarter of the resting energy requirement of an adult and irreversible brain damage results from interruption of this supply even for a brief period. Meltzer (Chemistry to Human Behaviour 1979) gives the figure as 10% to 20% of the total energy available to the whole body. This cerebral need is met almost entirely by the conversion of glucose to carbon dioxide and water. The blood cells also require a constant though very much smaller energy supply and their needs are met by the conversion of glucose to lactate, Resting muscle has a very low energy requirement which, it is thought, may come from the oxidation of fat. Vigorous exercise however is accompanied by a switch to the use of large amounts of carbohydrate as fuel. The liver, it is thought, may use the oxidation of amino acids as its own energy source.

The stores which cater for all this complex metabolism are the glycogen in liver and muscle and the triglycerides also to a small extent in the liver but mainly in adipose tissue. Protein is not stored as such but, if dietary intake is too low, tissue proteins will break down into amino acids and the vital organs will use this supply to maintain their tissues. In this situation muscle loss will usually be greatest.

An 'initially obese' individual can sometimes fast for some months without obvious ill effects but, in such a case, the brain and nervous tissue, which alone deplete the body of glucose since the lactate produced by the blood cells is

reconverted to glucose in the liver, will adapt their metabolic pathways to use increasing amounts of fatty acids.

Dietary intake is governed by - availability of nutrients

- appetite

- psychological drives or inhibitions

and in primitive societies the first of these must undoubtedly have dominated the pattern. For Western man to-day however food is abundantly available at all times and it might have been expected that one of the other factors, or a combination of the two, would take over control. Certain individuals, particularly if under forty years of age, do in fact, without a special effort, balance intake and output, maintaining what is popularly regarded as an acceptable adipose store but, for a percentage of persons at all age levels and for an increasingly large section of the middle aged population, excess storage is a problem. In our Western society therefore an appetite well matched to energy needs, together with a rather inefficient storage system, appear to be highly advantageous while a keen appetite and an efficient storage mechanism cause difficulties. Surely, though, man's higher centres should operate here! If excess adipose tissue is both cosmetically and physiologically undesirable (see Related Research - page 22) then intake can consciously be regulated so that for a while the body uses up the excess and afterwards an acceptable store is maintained. Unfortunately the homeostatic mechanism does not usually seem to operate in this way, at least not without considerable suffering on the part of the individual. Some would argue that low calorie diets actually stimulate a greater efficiency in their use (e.g. Berlan et al 1981) but Kral (1981) feels that there is as yet no real

understanding of feedback mechanisms in this area.

The problem of weight reduction or of overweight prevention has not yet been solved. For the extremely seriously overweight the effectiveness of jejunoileal shunt is marred by serious side effects (Baddely 1973, Moxley et al 1974, Frikini and Cassella 1974, Bray et al 1976, Finer and Pilkington 1980). Drug therapy has only a partial success record and is also accompanied by dangers (Malchow-Möller et al 1981). Diet restriction causes distress and, if it is to achieve its goal, usually needs to be supported by some sort of psychiatric measure, from clinically administered behaviour therapy to socially geared slimming clubs (Craighead et al 1981), which themselves may well produce, in addition to the weight loss, other questionable reactions. It has been stated that a period, during which the weight of a previously obese person is maintained at a desirable (?) level, can only be considered as a remission (Haber 1980), the implication being that eventually the weight will increase again and a real cure is rare.

Food restriction results in some uncomfortable physiological effects but the main disorder is psychological and it was the close observation of such temporary disorders in others and a personal experience of 'dieting' that provoked the writer's interest in the work of Watson (1972 - see page 52). Watson, working in psychiatry, found that a variety of mental ailments arose from consumption of the wrong (?) diet. The diet was not intrinsically wrong but was wrong for the particular subject in question. He divided his subjects broadly into two biochemical types, calling them slow oxidisers and fast oxidisers and he described two main types of diet that each should consume. Could the unconscious

search for the 'right' amounts of certain nutrients (or perhaps some trace substances) by a particular individual, inclining to one of his biochemical types but feeding mainly from the 'wrong' diet, result in overeating? Mental illness (caused in Watson's view, at least in many cases, by some measure of brain deprivation) might thus be avoided but obesity would not. Diet modification seemed an attractive alternative to diet restriction and the earlier work done by the writer, as part of this study, revolved around the possibility of grouping individuals according to Watson's criteria.

Distinction is drawn in the field between obesity of childhood onset (Forgett et al 1975) and that of adult onset (Kopelman et al 1979) and within the latter group between various stages of onset e.g. 'puppy fat' in adolescence, overweight following childbirth in females and the most common syndrome namely overweight that occurs as the basal metabolic rate lowers circa menopause (Eliot 1979, Noppa & Hallstrom 1981). Clearly obesity has no single cause.

A mechanism by which excess energy could be discharged from the individual system, thereby avoiding increase in adipose storage, was proposed by Rothwell and Stock in 1979 when they found that brown fat persists into adulthood in the human animal (see page 56). Differing efficiency of this brown adipose tissue could account for differences in the storage control of individuals and some thought was given to measurement of skin temperature over brown fat sites as a possible contribution to the assessment of biochemical 'type' (see NOTE Six)



In 1980 Margules postulated the famine and feast axis, antagonistic states (see page 43) and this theory somewhat extended the horizon of the writer, whose main drive was to question the idea of widely applicable specific cures for obesity (or come to that for anything else - see NOTE I). The emphasis now shifted from inherent difference of basic 'type' to difference of 'phase' in a naturally occurring rhythm. A few researchers, notably Margules, see the human animal as functioning rhythmically in a manner somewhat paralleled, in a more extreme form, by the hibernating animal. Within physiological functioning exist two states, one energy thrifty, primarily suited to a time of food shortage and the other, energy expensive, to a time of plenty. It is the writer's own thought that the slow and fast oxidiser types, described by Watson, could be individuals manifesting an incomplete switch from the feast to the famine states or vice versa but it is widely acknowledged, among those supporting the famine/feast theory, that an understanding of the nature of the switch from one state to another would make a valuable contribution towards solving the problem of overweight. There is a growing body of well supported theory concerning the nature of the hormonal control of these two states but as yet no published theories concerning the 'trigger' mechanism.

In many primitive societies the feast/famine cycle was annual and it is true Zahorska-Markiewicz (1980) has discovered a circannual rhythm. Weight reducing programmes she found were most successful in spring and least successful in winter with hospitalised patients who stayed in the same ambient temperature whatever the season. Production of heat by brown adipose tissue, while energy expensive, obviously has survival value in low ambient temperatures,

low ambient temperatures are in fact known to stimulate the metabolism<sup>of</sup> brown fat and this heat production, in very young or in hibernating animals was previously thought to be its only role. The seasonal occurrence of effectively cold conditions (see NOTE Two) is far from being world wide and, taking all this into account, it would seem that cold is an unlikely 'trigger' operator.

Chemical changes induced in the human body by the absence of food might well produce the 'famine' state but Margules postulate famine preparation, during which the economical storage of energy as fat occurs whilst food is still in plentiful supply. It is a highly speculative but reasonable hypothesis that in primitive societies a naturally occurring pre famine food substance acted as the 'trigger' inducing the 'famine preparation' state (see NOTE Three). Similarly another substance might in the 'towards the end of famine' diet have caused arousal. Possibly other substances, or their absence, maintained the 'famine' or the 'feast' state. These postulated substances would in all probability occur in a random, unpredictable, certainly non-rhythmic way in our present well processed, highly artificial diet, helping to cause, in some unfortunate cases, considerable imbalance.

Unfinished and unpublished work by Bray (reported by Elliot 1980) has begun to centre around diet modification and its effect upon the amount of brown fat. Sucrose and maltose apparently cause an increase and he hints that the protein content also exercises a control, although he does not state in which direction. Landsberg and Young (1981) have published work on diet-induced changes in sympathoadrenal activity and its implications for thermogenesis.

Anthropomorphic study could result in informed guesses concerning possible 'trigger' substances but systematic experimentation with diet (perhaps after tests for biochemical type or state) especially with respect to its vitamin or trace element content would be more fruitful. The success of Watson's diet changes given in accordance with his 'type' theory, the success of many unusual diet restrictions, supplements, combinations etc. is easily explained as the change itself supplying (by chance in many cases) the desired 'trigger' or ceasing to supply an undesired 'trigger'. Watson's investigations, preceding the diet change, clearly indicated which type of diet was required but most dietetic advice is less personalised. Nevertheless by accident some subjects might receive the correct trigger substance sufficiently often to change their 'state' while others are less fortunate. Such experimentation with diet should give some direction to detailed chemical analysis of food substances consumed in the search for an understanding of this postulated 'trigger' mechanism.

A recent radio broadcast (18.4.85) described work in progress at the Dunn Clinic. There they have devised a way to measure energy expenditure in human subjects without unnaturally restricting them. The subject receives doubly labelled water (labelled with stable isotopes of both hydrogen and oxygen) and goes about his daily life in the ordinary way except for supplying urine samples to the Clinic. Using a mass spectrometer the water and carbon dioxide output (i.e. the metabolic rate) is monitored and the energy output estimated. Experiments with different diets gives a measure of what minimum energy input is compatible with health. To their surprise they have so far come to the conclusion that a mere 20% above that required for basal metabolism will suffice. The prediction was that 50% would be needed. Their work is mainly directed towards the problems of food

shortage in mothers and babies in the third world but there are obvious implications for the obese in western society.

### III RELATED RESEARCH

In surveying current or fairly recent literature the reader cannot avoid the impression that there exist numerous elements, which can indeed be ringed into various, sometimes intersecting, sets but which rarely form proper links between each other, far less merge into a composite whole.

The population is always different, frequently, even if of the same species, having characteristics which prevent proper comparisons. The slant of the investigation or some vital detail in the technique is such that here again comparisons lack validity.

Valuable connections such as that made between Rothwell and Stock and the Dunn Clinic (see page 56) are extremely rare and, inspite of the many conferences held, the problems of obesity on the one hand and anorexia nervosa on the other remain largely unsolved.

It is not therefore easy to construct hypotheses, drawing support from research reports. A very real possibility of unrecorded variation seems to present itself in nearly every instance and, in cases where human subjects are involved, there are always questions needing to be asked. These may well be physically geared in a largely psychological investigation and psychologically geared in a physical study. It was inevitable therefore that there would be a certain amount of listing of work reported, this reflecting the need for broader based team research which should, in the view of the writer, precede the pursuit of fine detail.

### A. A CROSS SECTION

Several highly specialised journals and others of a more general character (e.g. Nature, The British Medical Journal, Hospital Medicine) have recently published research reports relating to obesity and energy balance but it is probably true to state that, not surprisingly, a cross section of current experimental topics can be found in the International<sup>al</sup> Journal of Obesity.

The following is a breakdown of the contents of this journal in 1980, 1981 and 1982.

#### Subject Content of Int.J Obes.

Topic	Vo.4 1980	Vol.5 1981	Vol.6 1982
<u>Experiment with drugs</u> (human subjects)	1 (dopa)	1(glomeruli filtration effects) 1 (ephredrine)	1 (review) 1(propranolol - effect on hypo-phosphatemia) 3 (weight loss with propanolane) 1 (side effects fenfluramine)
--	--	--	--
ditto			1 (ephridrine & brown fat)
(laboratory animals)	2(various)		1(peripheral actions) 1(catecholamines)
<hr/>			
<u>Energy balance experiments</u>	1(with fenfluramine also) 1(seasonal)	1(protein & fat changes) 1(with exercise)	1(with exercise in cool water) 1(blood pressure after weight loss)
<u>Degree of success</u> (human subjects)	2(different diets) 1(exercise effects on glucose tolerance) 1 (taste)	1(new formula) 1(behavioural control also)	1(physical working capacity after exercise & body weight reduction) 1(total fasting) 2(different diets) 1(palatability of foods)

Table 1

			1(hormonal effect of protein supple- ment)
			1(physical training)
			1(pattern of meal feeding)
--	--	--	--
ditto			
(laboratory animals)	2(different diets)		1("cafeteria" feeding)
			1(anti-obesity tri- glycerides)
			1(low palatability)
			1(carbo hydrates with exercise)
			1 (different diets)
--	--	--	--
<u>Evaluation</u> <u>using</u> <u>Metabolic</u> <u>Parameters or</u> <u>organ size</u> (human subjects)	1(general)	1(nitrogen balance)	1(nitrogen loss)
	1(smoking)	1(cate- cholamines in biopsy)	1(thyroid & others)
	1(thyroxine etc)		
--	--	--	--
ditto			
(laboratory animals)	1(general)		1(experimental obesity and plasma lipid)
--	--	--	--
<u>Evaluation</u> <u>from</u> <u>Adipocyte</u> <u>Examination</u> (human subjects)			1(adiposis delorosa)
--	--	--	--
ditto (laboratory animals)	1(general) 1(also comparison genetic)	1(after removal of fat pad)	

Table 1 contd

<u>Comparison</u> <u>Obese with</u> <u>Non-obese</u> <u>Using</u> <u>various</u> <u>parameters</u> <u>(human</u> <u>subjects)</u>	1(cortisol)	1(cardio-vascular risk)	1(general)
	1(thyroid)	1(health consequences)	1(immunological)
	1(Werner's syndrome)	1(weight for height in English children 5-11 yrs)	1(infant sensitive periods)
	1(adipose cellularity in childhood)	1(diabetes in Samoa)	1(effect of glucose on enzymes)
	1(skin temperature - early onset obesity of mature onset)	1(longitudinal infants and child weights)	1(peptide to insulin after glucagon)
			1 (gall stones)
			1 (salivation)
			1 (adipocytes in children 10-18yrs)
			1(serum lipoprotein in Japanese children)
			1 cell size and number and body fat)
			1(female fat distribution)
			1(pituitary and hypothalamic dysfunction in males)
			1(pseudo hypercortisolism)
			1(lymphocyte thyroid hormone receptors)
			1(cardiovascular risk)
			1(serum free tri iodothyronine)
			2(diabetes)
			1(glucose regulation)
			1(insulin)
			1(glucose intolerance)
			1(inherited effect on muscle cells)
			1(Apoprotein metabolism)
			1(hepatic steatosis)
			1(obesity associated disorders in non-obese)
--	--	--	--
ditto (laboratory animals)	1(gonadal hormones) 1(chromosomal)	1(oxygen consumption for assessing mass) 1(hypophagia and hypothyroidism in ob/ob)	3(general 1(enzyme difference) 1(membranes)
			1(hypothermia)
			1(NST and regional blood flow)
			1(increased protease activity in ob/ob muscles)

Table 1 contd



---

<u>Surgical Intervention</u> (human subjects)	2(General)	1(tubular proteinuria) 1(tridothyronine) 1(thyroid hormones in women)	1(sex hormones) 1(retinopathy) 1(general) 1(vitamin D) 1(vitamin A etc) 1(altered preference for fat & sucrose) 1(different types - barium meal evaluation) 1(phychosocial effects of gastric reduction)
--	--	--	--
ditto (laboratory animals)			1(anaerobic bacteria role in weight loss after bypass) 1(in Zucker rats)

---

Behavioural & Sociological  
Studies

(human subjects)	1(husband involvement) 1(remission not cure)	1(teenagers perception) 1(effect of obesity clinic) 1(locus of control) 1(comparison self reported height and weight with actual)	1(tolerance to frustration) 1(conditioning) 1(sociometric in school children) 1(obese adolescent)
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---

Theories

1(famine/feast)  
2(animal models  
proposed and  
needed)  
3(misleading  
height/weight index  
and its defence)

---

## Analysis of Topics in Int.J Obes.

Topic	% of 3 yr.total	Vol. 4 (1980) % of total	Vol.5 (1981) % of total	Vol.6 (1982) %of total
Drugs	10.7	10.7	8.7	11.3
Energy balance expts.	30.5	50.0	30.4	23.8
Comparison obese/ non obese	35.9	25.0	30.4	41.2
Surgical	10.7	7.1	13.0	11.2
Behavioural	7.6	7.1	17.4	5.0
Theories	4.6	0	0	7.5

Table 2

The balance between the types of research reported each year is not markedly different although it is difficult to know whether this reflects the balance between research topics actually being pursued or the editor's selection or chance completion of work. Volumes 4 and 5 also contain reports of papers given at conferences:-

see over page

Volume 4 contains eighteen papers from a Workshop on Nutrition, Behaviour and Life Cycle held in the U.S.A. in 1979. All contributions were from workers in the U.S.A. The work reported upon had not necessarily been completed.

#### Food Selection 18

Simoons was examining cultural, geographical, historical and religious influences on food selection, Blass, food selection in the aged, Stern, the genetic effect and also the effect of exercise and Hook, food selection in pregnancy. Wurtman was looking at the control of carbohydrate intake in young and in adult rats. Rozin in his first paper posed the question 'Why do we know so little about food selection?' and in his second discussed the acquisition of food preferences and attitudes to food. Wilson evaluated behavioural therapy and Rodin suggested that environmental stimuli may override biological regulation. Bartoshuk felt that there was a great need to investigate the sensory differences that resulted in variation in food selection.

#### Suckling 18

Blass and Henning were interested in controls over suckling in animals.

#### Babyhood Connections with Obesity 18

Kessen was attempting to forecast obesity by skin fold thickness in the newborn and Fomon had found a correlation between fatness at 112 days and 8 years but no correlation between fatness in later life and bottle or breast feeding.

#### Mortality 18

Andres was looking at obesity and total mortality.

#### Fat Cell Number 18

Faust thought that certain foods might increase fat cell number more than others and felt that there was a need to pursue this

enquiry further.

#### Feast and Famine ¶

Margules proposed his theory described in detail elsewhere.

#### Physiological Control ¶

Bray felt that more effort was needed to try to understand the mechanisms of the physiological control of energy balance.

There was no particular summing up reported and it is difficult to see how there could have been much of a finding since topics and subjects varied too much.

Volume 5 contains several similar reports.

The Royal Society of Medicine had held a Scientific Meeting in 1980 where Cawthorne and Arch had reported on drug investigations, James from the Dunn laboratory at Cambridge on defective or abnormal thermoregulatory processes in rodents and Silverstone from St. Bartholomew's on the effect of anorectic drugs on animal food intake. He had on going research on their effect in man.

There was also a Satellite (to the main Obesity Society) Symposium at Ischia in 1980 on Very Low Calorie Diets. This had obviously followed the deaths supposedly connected with this kind of treatment.

Howard from Addenbrooke's Hospital, Cambridge had found that these very low calorie diet did work but the weight loss was not maintained and Hickey<sup>cf P. 40</sup> from Eire reported that after eight weeks on the diet there was only 40% compliance among outpatients.

Contaldo, Italy, thought that there were some dangers for patients in metabolic wards. Apfelbaum, France, was studying nitrogen balance and felt that the diets were safe if the subjects were young and healthy. Blackburn et al U.S.A., reported on nitrogen sparing, a study that was in process. McClellan-Baird, England, was sure that some diets were safe and Zollner et al, Germany,

suggested a 300 K Cal diet using conventional food. Yang, U.S.A., had found that, using carbohydrate instead of protein, some patients showed more adjustment than others. Frank, U.S.A., had looked into the recent deaths but records were poor and the causes were therefore uncertain. He thought that there was chronic disease in 83% and felt that potassium and sodium lack were contributory. Cook, U.S.A., had not found that the anti-depressants, given during the very low diet period, were at all necessary. Quaade et al, Denmark were comparing the results of gastroplasty (the least mutilating surgery) with that of various diets and Atkinson, U.S.A., had found that non-physicians could supervise diets as well as physicians, saving them the "bore"!! Bray, U.S.A., had experimented with two commercial diets tried on rats, finding no difference between their effects. Wilson, Netherlands, had decided after studying the effect of these low calorie diets that there was a sub group of the obese that did not have hypothalamic dysfunction and Moore of Addenbrooke's, was looking at the role of  $T_3$  and its receptor in "efficient metabolisers" when on these diets. Bogardus, U.S.A., and Krotkiewski, Sweden, were involved in exercise connections with these diets. Rabast, West Germany, was particularly looking at thyroid involvement, Blondhein Israel, at thermogenesis, comparing 300 - 600 K cal with 800 - 1200 K Cal diets, Biase, Italy, at diabetes, Wechsler, West Germany and Schoten, Netherlands, at lipids and lipoproteins. Mancini, Italy, gave a paper on severe obesity and its medical complications.

The overall summing up of this conference was that these low calorie diets were a help and would survive recent criticism.

There was a Separate International Conference on Surgical Treatment in 1980.

There are now many techniques involving surgical intervention. The 'shunts' can be made in different locations and there is gastroplasty, which uses plastic meshes to reduce the absorptive surfaces, and vagotomy, which reduces appetite. The splinting of the jaw is less in favour. The summing up here emphasised the need for continuing research.

A Satellite Symposium on Adipose Tissue Development and Metabolism was held at Gottenburg, also in 1980.

There had only been ten years of active interest in this subject and findings were not yet such that they indicated treatment or behaviour modification, although presumably it is intended that these should eventually follow. The speakers included Tulp on brown adipose tissue.

Another Satellite Symposium on Hypertension was held in Florence in the same year.

Berchtold and Sims summed up here and their conclusions are mentioned elsewhere.

Many of the ideas and research programmes discussed at all the 1980 meetings are mentioned in the following sub section

The following table shows the geographical location of the researchers who reported at the international gatherings mentioned above.

## Location of Researchers at International Conferences

Location	Very low Calorie Diets 1980	Surgical Treatment 1981	Adipose Tissue Development 1981	Hypertension 1981
Argentina - - - - -	1			
Canada - - - - -			1	
Denmark - - - - -	1	2		
Eire - - - - -	1			
England - - - - -	2	1	1	1
Finland - - - - -			1	
France - - - - -	1		3	
Germany - - - - -	3		1	3
Israel - - - - -	1			1
Italy - - - - -	3	2		
Netherlands - - - - -	2			
Scotland - - - - -				1
Sweden - - - - -	1	3	6	2
Switzerland - - - - -				3
U.S.A. - - - - -	6	12	8	8

Table 3

## B. GENERAL SURVEY

In Garrow's revised edition of "energy Balance and Obesity in Man (1978)", it is stated that 20-30% of the adult population of Britain is above the "desirable" range weight for height and the prevalence of obesity is probably increasing. However, in Stunkard's and Stellar's more recent volume "Eating and It's Disorders" (1984), Hirsch and Leibel write "A seemingly inexhaustible supply of changing concepts regarding both etiology and treatment attest to our fundamental ignorance of the pathogenesis of obesity in man". Then, in the same volume, C and O Wooley mention "a shared unrest within the profession" and continue "The Question is whether the generally modest benefits of successful obesity treatment clearly outweigh the negative effects of unsuccessful treatment and the general impact, on an already weight-obsessed society, of our continuing efforts to prevent or eradicate fatness".

That particular problems are encountered by the female half of the population is reflected in a book, "A Woman's Conflict" edited by Kaplan produced in 1980. In it Anne Scott Beller deals with the connection of overweight with motherhood - 'while the role of female sex hormones in weight gain have never been clearly understood, there is good reason to suspect that they must play a major part in the process'. Another contributor Hilde Bruch writes of 'Thin fat people' - 'For many people overeating and being big may be balancing factors in a precarious adjustment to life' - 'there are people who function better when they are somewhat heavy'. There there are the 'thin fat people' - 'who stay reduced but who cannot relax: they seem to be as preoccupied with weight and dieting after they have become slim as they were before'. 'Anorexia nervosa is a rare disease: but one may think of it as the end state of the unrealistic preoccupation with weight and size that



Characterizes our society'.

So what is obesity and anyway does it matter?

# 1

## IS OBESITY PHYSIOLOGICALLY UNDESIRABLE?

### 1.1 Hypertension

The average general practitioner confronted by a middle-aged or elderly patient suffering from hypertension or heart disease will automatically order him to reduce his weight. In a paper, published in 1981, on the epidemiology of obesity, Berchtold et al described associations, some of which had been investigated during the Dusseldorf Obesity Study. Hypertension was the most frequent cardio-vascular risk in obesity. Normo-tensive obese were more likely to develop hypertension than those with normal tension and normal weight. Hypertension and age were associated in Western society but not in tribal society (where after 20 years of age there was no increase in body weight). They also refer to the work of Chiang et al (1969), who reviewed 39 studies of obesity and hypertension and found the association between them closer in women than in men and the Bogalusa Heart Study that found an association in children. The Dusseldorf study did however find that the effect of relative weight on blood pressure was rather less than the influence of age upon it. Nevertheless, the hypotensive effect of weight reduction did seem to suggest a close association.

Jung et al (1979) at the Dunn Laboratory, Cambridge, experimented with their patients, finding that a reduced carbohydrate intake produced a fall in metabolic rate, a reduction in cardio vascular indices of sympathetic activity and a fall in venous noradrenaline concentration but they expressed doubts about assessments made when, as is usually the case, there had been no attempt to ensure similar sodium intakes.

Larsson et al (1981) examined the effect of insulin and glucagon in obese, fasting, mostly hypertensive patients. This work supported previous studies indicating that insulin stimulates sodium reabsorption by the kidney and they concluded that not only sodium but also the carbohydrate content of the diet should be reduced in an attempt to induce negative sodium balance when trying to correct hypertension in obese subjects (see Landsberg and Young in next section).

Dunstan et al (1981) comparing 'hemodynamic and volume' characteristics of their obese and non-obese hypertensive patients, concluded that there was no indication that obesity affected the vascular system in any way that would result in hypertension.

Berchtold and Sims (1981) summing up in a joint paper on obesity and hypertension stated that there was some association but 'not every obese person becomes hypertensive' and as yet no association mechanism had been clarified, partly through lack of suitable reference standards for the measurement of obesity.

## 1.2 Thyroid

Sims (1981) reviewing the work of a number of researchers working with human subjects looked for connections between disturbed carbohydrate metabolism, increased sympathetic nervous activity,

increased activity of thyroid hormones and common sub types of obesity. He concluded that it was the metabolic derangement, rather than obesity per se, 'which was of importance'.

### 1.3 Fat Cells

Brook (1980) in a paper on 'The Fat Child' stated categorically that there had never been any evidence that 'the number of fat cells a person possesses makes the slightest difference to him'. This last statement also raises the question of the connection between obesity and the number of fat cells (see page 46). He concluded that 'there is little evidence that any but the most extreme obesity is of major consequence'.

### 1.4 Conclusion

Grinker (1974) challenged to define obesity gave 50-200% overweight as 'extremely obese', 25-50% overweight as 'moderately overweight', using Metropolitan Life Insurance tables but many would argue about the validity of using weight plus height alone. There is certainly little agreement about the exact definition of obesity. The general view with respect to the connection between obesity and cardio-vascular disorder is that there could be a common cause. If loss of weight alone results in a reduction in blood pressure and that weight loss is brought about by dieting, this does not necessarily imply a direct connection between the overweight state and the hypertension. Some workers claim a complete absence of evidence for a direct correlation.

Nevertheless overweight, whatever its connection or lack of connection with actual ill health is nowadays rarely a matter for individual satisfaction and frequently, in its more extreme forms, does cause physical discomfort. It is not difficult to justify research into its causes.

2

WHAT RESEARCH METHODS ARE FOLLOWED?

Research into human energy input, output and storage proceeds mainly along one of the following lines:-

- (i) experimentation with live laboratory animals
- (ii) experimentation with or close monitoring of live humans
- (iii) fact collection including questionnaires
- (iv) histological or in vitro investigations and/or experimentation.

Overlapping occurs when laboratory animals are sacrificed after experimentation in vivo and their tissues examined microscopically, their organs dissected or maintained and/or treated in physiological fluids. Rothwell and Stock's brown fat hypothesis arose from this type of investigation (see section E. ).

There is among the relevant literature evidence of a powerful urge towards detailed biochemical study which demands accurate and precise intervention on the part of the researcher but which may well have a gross effect upon the subject. Human subjects are therefore rejected in favour of lower animals. It is probably true to state that, apart from investigations connected with actual medical treatment, the bulk of all research into the problem of obesity comes either under (i) or into the overlap zone.

## 2.1 Work With Laboratory Animals

### 2.1(a) Sodium

Landsberg & Young (1981) were interested in the sodium content of diet (see previous section) when investigating hypertension in rats. They worked with 'spontaneously hypertensive animals' and they diminished calorie intake or withheld all nutriment whilst maintaining

normal sodium consumption and found that this lowered blood pressure. Conversely overfeeding sucrose, keeping sodium constant, increased blood pressure. Overfeeding on an iso-calorie ration of fat, instead of sucrose, had no effect on blood pressure. They concluded that 'the well known relationship between obesity and hypertension may, therefore, derive at least in part from an effect of dietary intake on the sympathetic nervous system'. This type of experiment could and apparently in the opinion of the Dunn laboratory (see above) should be undertaken with human subjects but much of the experimentation is rather more intrusive.

## 2.1(b) γ- amino butyric acid

There is a great deal of monitoring of hormone and other physiological substances in the live animal brain, using micro-electrodes inserted in certain areas and the connection between γ- amino butyric acid (G A B A) and the hunger (satiety mechanism is a very popular line of enquiry. Stellar (1980) and Ahlskog et al (1973) had established the hunger/satiety and hypothalamus link whilst Fahn (1976) showed that G A B A was highly concentrated in the hypothalamus and served as a neurotransmitter for this axis. Kelly and Grossman (1979) and Porrino and Coons (1980) found that micro-injections of G A B A or of G A B A ergic agonists elicited food intake and G A B A ergic antagonists inhibited food intake. The rats used for these experiments were normal but Orosco et al (1981) used animals that were hyperphagic because of lesions electrolytically inflicted on the ventromedian hypothalamic nuclei (VHN) and also used genetically obese rats from the Zucker strain. Jung et al in 1977 had discovered G A B A transaminase, a G A B A degradation enzyme, and Orosco et al used 8 - vinyl G A B A (Merrell) which preferentially inhibits the G A B A transaminase thereby increasing the amount of G A B A. These

two differing types of rat, VHN and the genetically obese, showed differing patterns of G A B A level in various areas of the brain but both showed the same acceleration of G A B A synthesis when compared with controls. G A B A does therefore appear to have an important role in obesity and food intake.

#### 2.1(c) Brain Lesions in General

Most workers produced brain lesions by electrolytic means but Mogenson et al (1977) found that 'the use of colchicine to produce a reversible functional block seems particularly appropriate for investigating the functions of a discrete neural pathway'. They felt that electrolytic methods clouded the issue by causing other effects in addition to the destruction of the actual target cells. Djazayery et al (1979) also produced lesions in the hypothalamus, this time of mice, using gold thioglucose and monosodium glutamate. His subsequent observations suggested that hypothalamic obesity was primarily due to decreased energy expenditure. Laughton et al (1980) produced his brain lesions in rats using bipiperidyl mustard and found that obesity also resulted but he could not discover the actual way in which the sympathetic nervous system was affected, although he thought that the route was via pituitary secretions, in particular prolactin.

#### 2.1(d) Central Nervous System Signals versus Signals from the Periphery

Novin (1976) found that response to glucose, which usually suppresses intake, changed, when various insults resulted in a lack of signals from the gut, liver etc. He believed that these signals were often as important as CNS signals.

#### 2.1(e) Serotonin

Wurtman (1980) used laboratory animals to establish that serotonin - containing neurones were involved in the control of appetite for

carbohydrates. He decided after this that mankind probably varied, some having an urge to eat anything and others an urge to eat carbohydrates, and that this difference might well be due to similar neurone differences.

#### 2.1(f) Sucrose

Lindley (1980) found that sympathetic activity was suppressed in fasting rats and stimulated if sucrose were given in addition to their normal diet. She felt that the hypothalamus integrated the changes and that insulin was an important link.

#### 2.1(g) Dopamine - - hydroxylase

Levin et al (1981), investigating alleged defect in catecholamine metabolism in genetecially obese Zucker rats, thought that dopamine - $\beta$ -hydroxylase might play an important role in the regulations of norepinephrine synthesis.

#### 2.1(h) Thyroid and Brown Fat

Many workers decided that thyroid hormones were inclined, at least, to stimulate brown fat activity and hence thermogenesis. Jung, Shelly and James of the Dunn clinic (1980) wrote 'Thus nutrition influences two major thermogenic hormones.  $T_3$  and noradrenaline. A fall in both on energy restriction would limit thermogenesis. There is also work of Danforth (see page 37). Burger writing in Life Science in April 1981 discussed the thyroid actions and reactions relative to this but came to no definite conclusions. Sundin (1981) explored the effects of thyroxine on rats at different ambient temperatures. He found that it appeared to reduce guanosine 5' - diphosphate binding in the brown fat mitochondria and hence lowered its heating capacity. He did not therefore feel that it was one of the substances responsible for the changes seen in the brown fat after cold adaptation

had taken place. Bray in 1981 discounted the connection between thyroid hormones and the thermogenic mechanism. He felt that intracellular nucleotides might be the operators of brown fat.

Since Rothwell and Stock (see page 56) together with sundry workers at the Dunn Clinic reported on the persistence of brown adipose tissue in the adult and on non shivering thermogenesis, this has been a favourite avenue for research, although it must be stated that Hirsch and Leibel (1984) claim that 'A great wave of excitement for theories related to defective thermogenesis has begun to ebb'. Apart from the thyroid connection mentioned above there is among others the work of Tulp (1981) which belongs to the overlap area. He progressively overfed a group of young rats until it was eating nearly twice as much as the control group. Body weight and body fat content increased only moderately but energy expenditure was doubled. The interscapular brown adipose tissue (I B A T) weight increased more than twice as rapidly as in the controls. It was found that, although the adipocyte diameter in both groups only increased by 30%, the adipocyte number tripled by 10 weeks of age in the overfed group. Moreover surgical removal of I B A T increased the efficiency of the weight gain. Previous work had shown that conditioning to cold increased the I B A T weight but that it decreased on return to warmer conditions. The I B A T increase due to overfeeding did not however decrease when normal diet was resumed. Propanolol which is known to block the thermogenic activity of brown adipose tissue did decrease the thermogenic response of overfeeding.

## 2.1(i) Brown Fat and Famine/Feast

Combining the brown fat idea with the famine/feast theory are Gunion and Peters (1981) who experimented with  $\beta$ -endorphin and



naloxone in rats. They confirmed that  $\beta$ -endorphin increased food intake whether injected in the lateral ventricle or in the medial hypothalamus and naloxone suppressed it. They concluded that brown adipose tissue made a major contribution to non-shivering thermogenesis (NST) and that NST contributed to seasonal adaptation. Brown (1980) had already found that rats given naloxone after a 24 hour fast consumed significantly less food and gained less weight than controls.

## 2.1(j) Essential Fatty Acid Restriction

A comment in the proceedings of the Nutrition Society (Sept. 1980) concerns the inhibitory effect on 1 L, 25 - dihydroxycholecalciferol-mediated calcium transport across the gut caused by essential fatty acid restriction and this was discovered as a result of work with rats.

### Fluctuation in Nutritional Intake

Barrow reported in Handbook of the Biology of the Aging (1977) research along quite a different line, not directly, connected with obesity as such. Using rats, fish, Daphnia and Drosophila he found that a period of underfeeding increased the life span. This does suggest that some fluctuation in nutritional intake assists healthy adjustment to life. He also fed two groups of rats the same calories but restricted protein in one group. Organ weights were not affected by the restriction and thymus involution was the same for both groups but body weight was lower in the restricted group and so was rectal temperature but oxygen consumption was higher.

## 2.1(k) Drugs

The commercial search for weight reducing drugs prompts much animal research. Comai and Sullivan (1980) treated rats with Pluronic L-101 and found that a decrease in body weight resulted

though there was no decrease in food intake. They were researching for Roche and found no resulting toxicity in their experiments.

Crawthorne and Arch (1982) researching for Beecham, experimented with varying, somewhat inconclusive results on bulk fillers (eg methylcellulose), intestinal modulators (neomycin, Bay g 5421, per fluo octyl bromide), metabolism modification (fen fluramine, amphetamine, diethyl propion, maxindol, phenterinine, acetylene dicarboxylate, and a hydrocitrae from the Indian gourd) using rats, mice and other laboratory animals. Blundell (1980) found that amphetamine inhibited hunger and so delayed eating but fenfluramine stimulated satiety so less was eaten. Stress overeating (achieved by "tail pinching" the animal) was blocked by fenfluramine but not by amphetamine. R & J Wurtman (1980) suggested that rats can be manipulated to select away from carbohydrate towards protein either by giving a carbohydrate rich pre-meal or by the use of drugs. Serotonin appears to control a specific satiety which defines the ratio of protein to carbohydrate. Fenfluramine blocks serotonin re uptake and seems to encourage the rats to eat protein.

More recently (1984) Blundell has discussed drugs such as amitriptyline, which in animals is associated with decrease in food intake whilst in clinical practice it has been reported as leading to craving for carbohydrate and to weight gain. This discrepancy he does feel may not necessarily represent a true drug-species difference. Rather it could be a result of the complexity of the food consumption control network.

## 2.1(1) Conclusion

Morley (1981), however, having worked with rats and after suggesting that the pro opiocorticotrophin molecule contains at least one potent bio-active pituitary hormone in addition to  $\beta$ -endorphin and ACTH, does comment that the biochemical interactions of man and

rats are often different. Not only are man and rats different but the responses of 'free living' rats may well show some variation from those of the laboratory bred animals, especially in an area that fringes on the behavioural. The gap between man and the unnaturally bred and reared rat may well be insurmountable in some respects. Bradley (1982) writes perhaps subject to dispute 'In lower animals weight gain depresses hypothalamic appetite such that dietary obesity is self limiting ..... Man, however, has a huge cortex that is dominated by psychological and social forces and he exists in a nutritional environment engineered to maximum hypothalamic and cortical appeal'. On the other hand the 'cafeteria fed' rats of Rothwell and Stock and certain aspects of laboratory life may give some reality to the analogy with man and the serotonin/protein/carbohydrate control is likely to be paralleled in the human to some extent at least.

Nevertheless, in 1977 Cahill was discussing "The big head problem" and concluded "Man's brain is so large and its activity so obtrusive that it is unlikely that any laboratory animal will serve as a satisfactory model for the long-term control of food intake in man".

A book published in 1976 'Food Intake and Chemical Sense', which is mainly a report following an international symposium in Japan, is largely concerned with invasive experimentation in differing species. Yet in the introduction Zotterman states 'tastes differ not only in different species but also in individuals' and 'De gustibus non est disputandum'.

Kare and Maller produced an overview of chemical senses and nutrition in 1977. They claimed that overpopulation of the planet, with consequent threat of food shortage, demanded a close study of chemical senses in order that efficiency in food production might be

increased, this "efficiency", in the main, consisting of the improvement by means of additives, of unpalatable nutrients. Some of their reports are of experimentation with gastropods, with cats and dogs fed with a variety of proprietary cat and dog foods, with rats etc. Their reports concerning humans are mentioned later (page 42). The researches had not, at the time of writing, given any clear indication of how they might attain their objective and the contribution of the animal experimentation is surely controversial!

## 2.2 Experimentation or Close Monitoring of Humans

Undoubtedly experimentation with or close monitoring of humans is much more valuable although hedged around with obstacles and drawbacks of no mean order.

Zaharska-Markiewicz (1980) is mentioned in the introduction as having discovered a circ-annual rhythm. Her hospitalised subjects in the same ambient temperature, whatever the season, slimmed most successfully in the spring and least successfully in winter. She thought that there was a seasonal oscillation in thermogenesis but felt that further study was needed.

### 2.2(a) Temperature and Metabolic Rate

Contaldo et al (1980) examined the left upper arm of each of his subjects thermographically. He felt that the area was not near any organs and not developed by occupation (presumably all his subjects were right handed) and therefore gave a more basic reading. He concluded that the lower temperature of the 'early onset' (obesity) group, compared with that of the 'mature onset' group might indicate a very sensitive way of demonstrating a lower metabolic rate in those with early onset obesity. Hancock (1981) was interested in core temperature and experimented with two subjects on a cycle-ergometer,

observing their recovery time but his main purpose was to compare values with simulated values (Fortram model of thermoregulation).

The relationship was not very close and he felt that this was due to the scarcity of possible core temperature measurement sites. He had measured rectal and tympanic temperatures. Using a "Uritemp bottle" Fox et al(1975) measured deep body temperature from urine and his results were, he felt, comparable to temperatures taken in the auditory meatus. The diurnal rhythm was better observed than when temperature was taken orally.

Werner and Reeuts (1980) mapped the surface temperature of the human body using thermocouples and they also measured the evaporation at six sites with capacitor moisture sensors. The back and chest did not show a marked difference from other sites.

Zaharska-Markiewicz (1980) measured the metabolic rate increase resulting from exercise in fasting subjects and then later repeated the measurement after a standard meal. Food increased the thermic effect of the exercise in eight out of ten of ten controls but only in four of the fourteen obese subjects. The small sample size is a difficulty here.

## 2.2(b) The Effect of Age

Stone & Norris (1966) did a considerable amount of work on the effect of aging. They looked at heat production (basal) first thing in the morning after having kept subjects in hospital all night and found a regression on age of  $0.93 \text{ calories/m}^2/\text{hour/decade}$ . Lewis's (1938) subjects came to hospital each morning and his figure was  $0.8 \text{ calories/m}^2/\text{hour/decade}$ .

In Finch's and Hayflick's (edit.) Handbook of the Biology of Aging (1977) it is concluded that 'fall in basal metabolism is simply a

reflection of the loss of metabolising tissue (or increase in body fat) with advancing age. The tissues in the elderly produce heat at the same rate as the young. Under resting or basal conditions body temperature of the elderly is the same as that of the young, 35-37°C.

## 2.2(c) Non-shivering Thermogenesis

Jung & James (1980) reported that patients with a propensity for obesity had a reduced drive for non-shivering thermogenesis (see III E). Lean subjects however produced much more heat when the environmental temperature was slightly reduced. A mixed food intake only stimulated heat production when it had a relatively high fat content. Starch or protein alone did not increase the thermogenesis. In 1974 Anderson et al had induced a reduction in the temperature of his subjects by exposing them to an environmental temperature of 20°C for two hours. Doi et al (1974) kept fasting young males, in cotton shorts only, at 10° for 90 minutes and found that the obese were much less responsive than the lean, who all increased their metabolic rate. Although Werner and Reeuts (see above) had not found any particular difference in surface temperature on the back or chest of their subjects. Rothwell and Stock (see 3(d)) had discovered increases over the back area when oral ephedrine had been given and James and Trayhurn (1980) showed increases in the inter costal area when noradrenaline was infused.

## 2.2(d) Blood pH and Age

Lewis (see above) also claimed that blood pH was maintained even in old age but adjustment was slower after an oral ingestion of  $\text{NH}_4\text{Cl}$  which shifts blood to the acid. Adjustment was effected in time however.

## 2.2(e) Steroids and Mood

Perhaps somewhat supportive of Watson's hypothesis (page 52) is work concerned with cortisol. Glucosteroids are well known to influence carbohydrate and protein metabolism and cortisol is, in man the most active steroid in this group (Bell, Emslie-Smith and Paterson). Its secretion shows a marked circadian rhythm (highest just before waking and lowest during the early hours of sleep) but stress appears to cause a considerable rise. Scapagnini and Nistico (1978) found an increase in plasma cortisol in depressed patients, suggesting that monitoring the levels might be a guide to treatment. However, this does not appear to be very new as Pollit in Psychological Medicine For Students (published in 1973) mentions a connection between cortisol levels and depression, a correlation between fall in the level and recovery having been shown. Also the diurnal variation is in phase with the morning accentuation of symptoms found in depression. Scapagnini and Nistico found a high positive correlation with hydroxycortico steroid (17-OHCS).

## 2.2(f) The Endocrine Approach

### 2.2(f) Childhood

- i Kopelman et al (1979) suggested that obesity of childhood onset was associated with hypothalamic abnormalities, the evidence for which was a reduced prolactin response to insulin hypoglycaemia. It was rather surprising to find that Karlberg had given noradrenalin to babies and had found a from 15-56% increase in oxygen consumption.

### 2.2(f) Adults

- ii Glass et al (1981) in a comprehensive paper on 'Endocrine Function in Human obesity' reported significant difference

in cortisol, growth hormone, prolactin (only after chlorpromazine), cf Kopelman, insulin, parathyroid hormone, serum endorphin, aldosterone (only after furosemide) and plasma norepinephrine metabolism. In many cases the metabolism returned to normal after weight reduction and the degree of metabolic difference correlated with the degree of obesity. They concluded their survey '.... it is likely that the obese population is heterogeneous with regard to the pathogenesis of the obesity'. Whether the concurrence of hypothalamic - Pituitary dysfunction and excess weight gain in obesity also reflects underlying hypothalamic pathology in a sub group of the obese is an unanswered question of critical importance to the rational management of millions of overweight patients?

## 2.2(f) Thyroid Involvement

### iii

Danforth (1981) overfed lean human subjects and observed increased metabolic clearance and production rate of  $T_3$  (thyroid hormone), although  $T_4$  was not affected. He found that sympathetic activity increased 'through a metabolic signal common to both overfeeding and carbohydrate intake, possibly elevated insulin concentration induced by these manoeuvres'. Unlike Zahoraka-Markiewicz (1980)(a) he did not find in his lean individuals an increase in energy used in exercise. He felt that the non shivering thermogenesis of his subjects was 'expressed as an elevation of the resting metabolic rate'. He stated that 'Man is a periodic eater and a constant metabolizer' as quoted in Introduction and went on to suggest certain 'wasteful' metabolic loops whereby energy could be lost as heat. He concluded 'Evidence is presented that diet regulates these hormones (i.e. thyroid and catecholamines - see Jung, Shetty & James page (28)). Decreased intake of calories



decreases and increased intake increases their metabolism. It is hypothesized that diet induced alterations in these hormones represents a physiologic adaptation, important in survival in times of feast or famine, which tends to blunt the ease of loss or gain in weight, through regulation of energy expenditure. He did conclude that thyroid hormones might control the capacity of the brown fat system to respond to the sympathetic nervous system through the control of the number of brown adipocytes or through synthesis and degradation of the purine nucleotides and the mitochondrial proteins of the brown fat adipocytes.

Also further to the thyroid hormone discussion (Glass et al) (1981) in the paper referred to earlier state that there is no evidence for any clinically significant abnormality in serum thyroid levels or in the function of the hypothalamic pituitary thyroid axis in obese subjects. The administration of thyroid hormone causes a loss of lean body mass rather than fat.

## 2.2(g) Drug Treatment

Craighead et al (1981) undertook clinical trials with 120 patients (and a waiting list used as controls) of fenfluramine hydrochloride (see Crawthorne & Arch (page 31) alone, the drug with behaviour therapy and behaviour therapy without the drug. The treatment was continued for six months at the end of which the 'drug plus therapy' group was best, although all had lost weight. All subjects were seen again at the end of a year and then all had gained weight but the 'therapy alone' group had gained least. Douglas (1981) as a result of his drug trials thought that most anorectic agents decreased food intake by interfering with brain monamines but fenfluramine (see page 31)

operated via the serotonergic pathway. The catecholamines increased thermogenesis but had toxic side effects when given as drugs.

Karsager (1980) administered gentamicin to his obese patients and found that it was taken up by the adipose tissue. Smedegard (1981) treated, with what he regarded as only unimportant side effects, 21 patients for about 12 weeks with a daily dose of Femoxefine (a phenyl piperidine derivative that potentiates serotonin). Blundell (see page 31, previous section) warned that the food consumption system is vulnerable to nonspecific drug influences and suggests "a continuous and more rigorous approach to the use of pharmaceutical agents lacking any intended action on eating and hunger". Cawthorne & Arch in their report on drug treatment, referred to above, asked "Is it possible that obese people produce excessive amounts of endorphins?" They then reasoned that if they did it would follow that they should be less sensitive to pain.

## 2.2(g) Pain

i

They then reported that 'Science' 202 988-990 carried a report concerning endorphins (Margules et al 1980) and suggested the nociceptive flexion reflex as a test as this correlates well with a pricking sensation (Willer et al 1976)

## 2.2(h) Surgical Insult and its Complications

Palombo et al (1981) found that urinary creatine excretion could serve as a means of estimating lean body mass in his morbidly obese patients who had suffered surgical bypass operations. He discovered no evidence for protein malnutrition or hepatic dysfunction.

The most drastic human experimentation is, of course, the jejunoileal bypass technique and other similar gut interference measures. Koopmans & Sclafani (1981) found that the operation's success in

producing weight loss was connected with changes in the lower gut signals. He stimulated the terminal ileum with a nutrient rich chyme. A preliminary report in 1983 on "gastric banding" by Bø and Madalski claimed that the method was safer but there can have been little time to assess other than immediate difficulties. Sclafani (1981) found that the bypass reduced taste and sometimes produced anorexia and taste aversion. Kral (1981) reviewed the effects of these operational measures, including the 'general upset' after vagotomy, another dangerous measure. Removal of fat is only palliative and dental splinting has little to recommend it.

## 2.2(i) Behavioural Emphasis

A certain amount of temporary success was obtained by Jordan (1981) who directed 1056 volunteers by post to keep diaries and to try various behavioural techniques and various types of foods etc. The weight loss was measured at meetings.

The writer in an earlier investigation (1972) recorded the restricted diets, fat fold measurements, body weight and, in some cases, body potassium counts of members of three different types of slimming club, patients in three residential institutions and some persons without affiliation and found that success in slimming correlated with the degree of power in the external control i.e. the patients with the least freedom did best, the unaffiliated group did worst. Exceptions to this were the writer and the research worker who took the potassium measurements. Here a powerful scientific motivation overcame the lack of external control and diets were adhered to meticulously and weight loss corresponded exactly to prediction. There did not in general appear to be a potassium loss concurrent with weight loss, although the results were somewhat ambiguous and a few subjects were

reluctant to repeat their experience inside the Whole Body Counter.

It was possible to write after assessing this work 'a connection between calorie intake and weight and body fat ..... the detailed records and measurements of the writer and one other subject provided compelling evidence of the closeness of the connection? Nevertheless it was also necessary to report certain subjective symptoms e.g. 'constant sensation of hunger throughout causing restlessness and diverting attention from non-routine, non manual tasks, tendency to think about food excessively, tendency to constipation, tendency to indigestion etc.

## 2.2(j) Humans and Chemical Senses

The tastes, textures and odours of food (plus to a much lesser extent its colour and shape) are the main contributions to the pleasure of eating and the pleasure of eating itself has close correlation with the amount of food consumed.

The editors of 'Food Intake and Chemical Senses' (1977) Katsuki, Sato, Takagi and Oomura, attempt to describe the electro-chemical pathway to the higher **olfactory** and gustatory nervous system but Acker and O'Regan (1983) and again Pallot (1982) have produced books exploring the role of the peripheral arterial chemoreceptors, the carotid and aortic bodies, which, although nothing is proven, provide basic work for further study.

However, Plattig and Kabal in 'Food Intake and Chemical Senses' report on attempts to measure comfortable and uncomfortable **alfacting** and taste sensations by electro encephalograms. Miller Jr in the same publication concludes from similar testing that 'friction and movement increase stimulation of taste buds', thereby verifying a commonly arrived at conclusion from common experience! Dental research not

surprisingly frequently concerns itself with the 'sweet preference' and some workers at a conference in 1974 seemed to conclude that the obese were more discriminating but avoided sucrose, nevertheless eating more of nice tasting food. Grinker (1974) said 'Although diet palatability may be a factor in overeating, we would conclude that it is not a major factor in the etiology or maintenance of the obese state ..... early obese show hypercellularity and hypertrophy of adipose deposits ..... perhaps early dieting intake has an important role'. Stellar at the same conference commented on his lack of surprise that different methods yielded different results. 'Different methods' he said 'reveal different parts of a complex mechanism'.

Those who make profits in the food industry would doubtless be interested in 'Intensity and Hedonic Functions' (Moskowitz 1977) and the likelihood that 'Hedonics and sensory interests are highly correlated for some chemosensory stimuli (especially those which are principally unpleasant) and only moderately correlated for others (those that reach a peak pleasantness in the mid range of concentrations and then decline)'.

Naim and Kare (1977) write of the commonly recognised effect of oral stimulation on the activity of the whole gastrinal tract but most of the work in this area is with laboratory animals. The involvement of amino-acids in food selection and intake is obviously a very important matter which Rogers and Leving (1977) review but again most experimentation was also with laboratory animals. In writing about monosodium glutamate Cagan (1977) fails to forecast the more recent suspicions as to its sinister character and Gershaff's (1977) examination of the role of vitamins and minerals in taste, while inconclusive, opens up what might well be a more fruitful line of enquiry. However, the factors which control the chemical sense/obesity

axis are many, nutritional state, immediate environment, social attitudes and social pressure, intellectual perception, state of health, early indoctrination, early feeding pattern, habit, mood etc. All of these vary from individual to individual and, within the same individual, some of these vary from hour to hour. An 'average' measure of sweetness perception and a 'mean' preference evaluation may be important, as commented earlier, to food manufacturers but it is difficult to see how it helps the overweight individual, whose own personal individual complex preference pattern affects (possibly even overrides) the factors listed above. It is of course, widely appreciated that monotony in diet causes the appetite to flag, although, as Lepkovsky (1977) writes, bread can be offered continuously without causing aversion. He also comments on the connection between taste preference and nutritional value. 'The highly developed brain of Homo sapiens is at odds with nutritional biology.

Dethier (1977) concludes 'There is no doubt that behavioural responses to food are determined by the net result of central neural integration of multiple sources of information from the external environment and the internal milieu. The possibility remains, however that changing internal states alter directly the responsiveness of the chemosensory systems themselves.

## 2.2(k) Exercise and Energy Balance

Careful measurements have been made, using calorimetry and respiratory quotient estimates of the exact numbers of energy units used in order to perform certain standard tasks and it is clear that a very long brisk walk would be needed to overcome the adverse effects of one sinful bar of chocolate or one cream cake! Nevertheless, Garrow (1978) concludes that there is 'meagre evidence' in this area but 'exercise may have a disproportionate affect on preventing obesity'.

There is clearly only a small effect on energy output but an exercise programme 'may subtly effect lifestyle in a way difficult to measure'.

The topic of energy waste is relevant here too. Hegsted (1977) writes 'I predict that we will soon be able to show that a calorie is not a calorie but that it depends upon the source of the energy, the metabolic state of individual receiving the energy and the idiosyncracies of the subject himself'.

## 2.2(1) Conclusion

Clearly the answer to the problem of overweight is not calorie restriction alone, nor yet drugs or surgery which often have undesirable side effects. It is undeniable that any calorie restriction, if sufficiently severe, will, with any subject, produce a loss of weight but, as mentioned in the introduction, rarely can this loss be maintained for any length of time. Even rarer is a psychological adjustment to the lower calorie intake. Sims (1981) commenting on the thyroid hormones and sympathetic nervous activity writes 'An adaptive mechanism which would conserve expenditure of body fuels in times of famine and which would enable the expenditure of excess calories, when overeating, perhaps to gain enough of an essential nutrient, would have obvious survival value? If the overeating is in fact a response to the body's need for an 'essential nutrient' then diet restriction could cause real physical deprivation and, if the brain, as a result of this, is deprived then psychiatric effects are likely to follow.

## 2.3 The Statistical Approach

A statistical approach to data obtained during interviews, from records or from questionnaires (iii) is frequently encountered sometimes combined with experimentation.

### 2.3(a) Connections with Health

Berchtold et al (1981) investigated the connection between obesity and hypertension. They found that both were associated with age in Western civilisation but not in tribal societies where age and an increase in weight were not themselves associated. Chiang et al (1969) had already found an association, closer in women than in men (see earlier page 22). Apparently Berchold et al also found that the black population had higher blood pressure levels than the comparable white population. Dunstan (1981), as mentioned earlier, did however decide after her analysis of statistics concerning obese and non obese hypertensive patients that they did not differ in any way 'that would indicate that obesity confers a unique aberration on the vascular system that results in hypertension. Also Berchold reporting subsequently with Sims, giving conclusions and recommendations, admitted that the mechanism of the association had not yet been clarified.

### 2.3(b) Class and Marriage

A rather different type of study by Hallström (1981) found upward social mobility negatively associated with obesity and also in association with Noppa (1981) discovered that 'never married' women showed more tendency to weight gain and to excess weight.

### 2.3(c) Teenage Perception

Worsley (1981) tested teenagers perception of fat and thin people and concluded, not very surprisingly, that 'stereotypes of obese and slim individuals are related to sex, ethnicity and self concepts of the perceiver' (!)

## 2.4 In Vitro Studies

### 2.4(a) Roncarì's Cells

The most interesting of the great wealth of in vitro studies (iv)



is Roncari's (1981) model derived from work with his cells. He had previously successfully established a propagating cell culture. He found that Estradiol significantly enhanced replication of cultured human omental adipocyte precursors. Androgens did not influence replication and he concluded that 'obviously estrogens partly account for certain adipose tissue changes at puberty'. He also found that under certain circumstances a negative energy balance elevated the lipoprotein lipase activity of fat cells. He suggested that 'This might counteract the fat cell reducing effect of the negative energy balance making weight reduction and weight maintenance more difficult'. The catecholamines were found to be the most important stimulators of lipolysis and there was increased lipolytic response following physical training and in hyperthyroidism (cf comment re thyroid hormones page 24).

#### 2.4(b) Sodium/Potassium Pump

Many reviewers also regard the work done by De Luise et al (1981) as having important implications. They found that the red cells of obese people had fewer sodium/potassium pump units. The higher sodium concentration inside the cells persisted after loss of weight.

#### 2.4(c) Fat Cells

A combination of observation of dieting humans and histological observation of specimens of fat cell tissue enabled ~~a number of workers~~ to state that once a fat cell had been produced it remained with the individual for life but fat cell size could be reduced by dieting. There is however, a certain amount of doubt about the validity of this finding. In fact the work of Van (1984) suggests that 'contrary to

previous beliefs which invoked a static complement of fat cells after maturation, the new concepts emphasize that adipose cellularity is more dynamic than was once thought.' He had identified, in culture, cells which could have been adipocyte precursors or delipidated once mature adipocytes.

#### 2.4(d) Obesity and Disease

Lafontan and Berlan (1984) described novel microscopic techniques -freeze fracture scanning electron microscopy, visualisation and/or labelling of hormone binding sites. They felt that considerable progress had been made towards 'elucidating the action of insulin and the sub-unit structure of the insulin receptor.' This raises once more the matter of an obesity and disease connection. Van (1984) confirmed that catecholamines were direct triggers for the lipolytic process and their effect was antagonised by insulin but steroid hormones might well have a regulatory effect and sex hormones could play a part. It did seem from his investigations that fat cell size in the abdominal region and the circumference around the abdomen showed the strongest correlation with metabolic disturbance. Obese men are therefore, it would seem, at a higher risk than obese women for development of cardiovascular disease because abdominal fat cells have to store lipid in a labile way and this causes them to be more sensitive to lipolytic stimuli. More free fatty acid than is needed is liberated by these cells and this affects the liver, giving rise to various disorders, including diabetes mellitus and possibly hypertension. Women in general have more fat in the gluteal/femoral region and less in the abdomen.

#### 2.4(e) Human Measurement

In vitro studies have therefore, especially more recently, given some basic indications for human macro-investigation and for the management of obesity. It is suggested by Van's work that abdominal

circumference should be measured as well as weight when the connections between obesity and disease are studied.

#### 2.4(f) In Vitro cf In Vivo

Vernon and Clegg(1984) have tried to compare in vitro findings with in vivo results. Obtaining the best experimental animal for the live experiments, namely the Syrian fat tailed sheep, is difficult so the inguinal pad of the female dog was used instead. The vascular supply was isolated and perfusion experiments performed. By comparison with in vitro observations the effects of various substances and also of stress were deduced. Seelbach et al (1984) looked at the fat cells in Zucker rats after experimenting with lean and obese strains, causing them to take vigorous treadmill exercise for ten weeks. There was only a 12% decrease in fat in the obese. They had fewer adipocytes but their size was not affected. The lean, on the other hand, had a 32% decrease and their adipocytes were smaller. This seems important in many ways but Seelbach et al lay their main emphasis on the fact that exercise did not normalise body composition in obese rats.

#### 2.4(g) The Evolution of Adipose Tissue

In looking for the causes of difference between obese and lean humans, it is interesting to study the evolution of animal cells and of adipose tissue in particular. Clues may well be found in the physiology and behaviour of other species. Pond (1978) has investigated the effect of seasonal variation, age and sex on the deposition and reabsorption of fat in a great number of species. She wrote '...many carnivorous birds and mammals make caches of excess food to which they may return later: the energy expended in returning to the caches and the risk that food will be decayed or removed apparently detracts from fitness less than does obesity.' This yet again raises obesity health issue. Subcutaneous fat, Pond thought from the data (and her own contribution is considerable), appears when all internal deposits have been filled up.

In the wild it is only massive for short periods .

The distribution of fat in humans is, she has found, atypical among mammals in quantity and location and in its close correlation with age, sex and race. Nevertheless the deposition of fat at certain sites as sexual signals, though different human from non human, is common to many vertebrates.

The measurement of subcutaneous fat in Canadian Eskimos, she feels, suggests that its distribution has little to do with thermoregulation.

Later work by Pond (1984) suggests that species that are strict vegetarians often have large fat cells, while many with small cells are strictly carnivorous, omnivorous species having intermediate sized cells.

Pond is interested in the evolutionary/embryonic connections with adipose tissue and the relationship with lactation. The tissue mass will of course vary with the nutritional state of the particular animal at the particular time of examination and this makes for identification difficulty. She has looked at cell volumes at many sites in many animals, her specimens having come from a number of zoological gardens, from laboratory colonies and also from the wild.

She concludes that adipose tissue shows a clear anatomical organisation in mammals with homologous sites containing cells of similar size in different species. Also she thinks that mammalian organisation of adipose tissue arose primarily in connection with its role in promoting the evolution of lactation.

### C. DISCUSSION

Presumably much of the research in this field is aimed at eventual intervention to modify body processes, either directly by drugs (even perhaps by surgery) or indirectly through modification of behaviour, with the ultimate goal of improving the lot of man. Comparatively speaking man is undeniably a complex creature and research into this complexity is greatly handicapped by the fact that it is man himself that is doing the observing and the experimenting. Where the investigation is for pure knowledge alone then it can be said that the various biochemical in vitro experiments, histological examinations, analogous study of intervention in laboratory animals etc. are very interesting and many of the results are significant, although fragmentation detracts even here. Where the purpose is man's welfare then it is difficult to see how the present lines being followed with great precision and with close attention to detail will, in the not too distant future, lead to happier ways of treating the overweight individual. Drug therapy even at its most cautious, is really no more than a vague thrust in the dark and is consequently because of its interventive potential (for good or ill) dangerous. Dieting is safer and a sufficiently restricted diet will undoubtedly reduce weight in practically any patient but the accompanying psychiatric effects strongly indicate undesirable cerebral deprivation. Diet change, of a not too extreme kind with the possible cautious, well monitored experimental addition of a succession of vitamins, each patient being assessed and advised on an individual basis, might well prove more successful.

Fashionable concepts of desirable weight are, in many cases, unfortunate in their effect and the real connection between overweight and ill health needs much closer investigation, using large scale

surveys of medical statistics and longitudinal studies of individuals.

In general it seems logical to suppose that research on a very broad front would, in this area, have more success than the isolated investigations now in progress. Publication of results certainly offers the possibility of interchange, overall survey and linkage between findings but only after considerable delay. The social and to some extent the physical environment is now in a state of flux and mankind is no doubt responding with a variety of temporary adaptations. By the time deductions are made from long past work, they may no longer apply. Constant interaction between all main researchers in the field, as would happen in a broadly conceived large team project, is highly desirable.

Stellar (1980) in a paper entitled Perspectives on Nutrition and Behaviour from a Neurological Point of View suggests the following research needs:-

1. Investigation of neural mechanisms,
  - (i) Signals from fat cell size and number that control intake and fat metabolism,
  - (ii) Anorexia - still unknown neurologically inspite of the limit of its occurrence to young females,
  - (iii) the overweight of middle age.
  - (iv) the role of exercise in changing the internal environment and therefore the brain.
2. Studies of the role of peptides in food selection and the regulation of intake following work by
  - (i) Margules and B-endorphin (see ~~IIIF~~),

(ii) Smith (1975) and cholecystokinin, part of the satiety mechanism,

(iii) Bryant and angiotensin, which increases water and salt intake, especially with regard to how this substance influences the brain (and which part)

### 3. The influence of diet on brain function and behaviour

(i) the effects of early malnutrition on intelligence

(ii) the direct influence of specific nutrients on brain chemistry and mood, effect and behaviour.

(Some progress has been made on these fronts).

Kety (1978) in The Biochemistry of CNS and Behaviour indicates the delicacy of the interweave of biological systems.

'It had become increasingly clear in the past decades that in the function of the synapses of the brain one is more likely to find the basis of higher nervous activity. It would be expected that in these switching mechanisms might lie the difference between sleep and wakefulness, rational and irrational thought, depression and elation. When it became clear that synaptic transmission was largely a chemical process, a basis was provided whereby bio chemical changes of even a small and localised nature could have crucial effects upon behaviour and mental state'.

More recently (1984) Van Itallie has suggested that slimming might deplete body protein and the drive to overeat may derive less from the need to fill empty fat cells and more from a need for more protein. Also Crisp (1984) has investigated Anorexia Nervosa finding that its essential characteristic is 'low and prepubertal body weight maintenance, rooted in a fear of normal body weight' and Fairburn (1984)

has looked at a newly defined entity called Bulimia (binge eating).

So far suggested treatments are largely behavioural in their approach.



D. SLOW AND FAST OXIDISERS

Differences in Intermediary Metabolism in Mental Illness

In 1972 Souvenir Press published a popular medical book by George Watson called 'Nutrition and Your Mind'. The following is a quotation from the inside of the dust cover of this book.

'Dr. Watson explains in detail the fundamental knowledge we have of metabolism and through a series of case histories illustrates its relation to mental health. He is, of course, at war with psychotherapy, which generally refuses to take these physical facts into account. Contrary to the therapists, Watson believes that much erratic mental behaviour has no 'meaning' or 'motivation' at all, that it is simply the result of an exhausted nervous system, an undernourished brain, an obscure allergy, an absurd reducing diet, an imperfectly functioning body, or any of a host of other physical problems, none of which is likely to respond to psychotherapy. The cure, naturally, involves finding out the real source of the trouble '

At the end of the book is a reprint of a scientific report entitled 'Differences in Intermediary Metabolism in Mental Illness', produced under the auspices of the Lancaster Foundation for Scientific Research. Watson had found, during a twenty year involvement with mentally ill patients and as a result of experiments designed to expose enzymatic blocks that might be causal factors in the illnesses, unexpected worsening of the ailment in some patients, following treatment with certain vitamins and minerals. Subjects showing similar symptoms, paired for age and sex, responded very differently to the vitamins etc., some showing definite improvement, others experiencing exacerbation.

Subsequent blood studies showed significant differences between patients who had been classified, from their reactions to certain vitamins etc., as Type one and those who were Type two. Plasma pH and dissolved carbon dioxide showed the best correlation with the vitamins (and other substances) classification.

The substances are listed below :

	<u>Type 1</u>		<u>Type 2</u>
favourable responses to	Vit D Vit K	favourable responses to	Vit A Vit E
	Ascorbic acid		Vit B <sub>12</sub>
	Biotin		Niotinamide
	Folic acid		Pantothenic acid
	Pyridoxine		Choline
	PABA		Inositol
	Riboflavin		Citru Bio-flavonoid Complex
	Thiamine		
	Iron		Calcium
	Potassium		Iodine
	Magnesium		Phosphorous
	Copper		Sodium
	Chloride		Zinc
	Manganese		

Watson then experimented upon twenty mentally ill subjects, observing them over a period of eight months. Ten were Type 1 and ten Type 2 (classification now being made from plasma pH-7.47 or higher for Type 1 and 7.45 or lower for Type 2).

The subjects were given the following formulae in capsule form, three times a day after meals and therefore received some dangerously high doses.

Type 1

Vit B, 10mg  
 Vit B<sub>2</sub> 10mg  
 Vit B<sub>3</sub> 10mg  
 PABA 25mg  
 Niacin 25mg  
 Ascorbic acid 300 mg  
 Vit D 2500 iu  
 Potassium citrate 900mg  
 Magnesium chloride 100mg  
 Copper gluconate 0.6mg  
 Manganese oxide 10mg

Type 2

Vit A 25000 iu  
 Vit E 100 iu  
 Vit B<sub>12</sub> 10 mg  
 Nicotinamide 200 mg  
 Pantothenic 50mg  
 Choline 300mg  
 Inositol 90mg  
 Bioflavonoids 350mg  
 Calcium 330mg  
 Phosphorous 250mg  
 Iodine 0.45mg  
 Zinc Sulphate 10mg

Their improvement was graded as :-

clinical remission of symptoms	-	11	showed this
marked reduction in intensity of symptoms	-	5	" "
noticeable " " " " "	-	4	" "

(Watson regarded the actual manifestations of the mental illness as of little importance diagnostically. He was less concerned with whether a patient displayed the symptoms of schizophrenia or mania or depression and much more interested in the intensity of the disorder and the blood analysis).

During treatment the biochemical variables of this group also changed. At the start of the experiment Type 1 had an average pH of 7.54 and at the end it was 7.43. The Type 2 group had a starting average of 7.36 and a concluding pH of 7.46.

These results led Watson to the hypothesis that Type 1 individuals were 'slow oxidisers' whose 'poor utilisation of carbohydrate and glucogenic amino acids resulted in a slow but preferential utilisation of fats and ketogenic amino acids and

for these he would prescribe in plenty

sweets, jams

potatoes, rice, cereals, bread, pasta

salads

milk, cottage cheese, eggs, white fish

Type 2 individuals, on the other hand oxidised carbohydrate and glucogenic amino acids too rapidly and they were advised to eat plenty of the following:

pastries high in fat

avocado, beans, peas, cauliflower, spinach

liver, kidney, meat concentrates

lard and butter

These foods plus the vitamin supplements mentioned above supplied, according to his theory, the necessary enzymic and co-factor needs to harmonize the biochemical cycles and therefore produce a better energy supply to the brain.

Watson had of course disregarded some quite well documented evidence of 'mind over matter' and it may well be a chicken and egg' situation since psychotherapy could conceivably affect brain chemistry. There are in fact some reliable accounts of this happening. Nevertheless when the best point for intervention in a cyclic situation is considered, his approach is very attractive.

The writers original theory postulated some obesity as arising from over consumption of calories in the pursuit of certain nutriments (see Sims (1981) in Related Research p 27 ). The mental symptoms would be kept at bay by this overconsumption but diet restriction might well result in psychiatric disturbance. Both the overweight and the mental symptoms could possibly be avoided if diet were adjusted to 'type'.

E. BROWN ADIPOSE TISSUE

A role for brown adipose tissue in diet-induced thermogenesis

Arousing sufficient public interest to provoke a television documentary on the subject was the work of Rothwell and Stock, Dept. of Physiology, Queen Elizabeth College, University of London, who published their findings in Nature of September 6th, 1979.

They had studied the controversy concerning the role of diet induced thermogenesis (DIT) in the regulation of energy balance.

Blaxter had felt that it was relatively unimportant whilst

Miller had seen it as central. Rothwell & Stock decided that

the controversy arose from 'the experimental use of abnormal animals and diets to produce differences in energy intake'.

They developed a regime which resulted in voluntary overeating of a balanced diet in normal animals, a 'cafeteria' diet.

Rats were offered their normal stock diet, on which they appeared to control their intake precisely but in addition they were presented with four attractive, high calorie content, new food items. In this way the animals were induced to overeat and became obese. When the palatable foods were removed they rapidly returned to normal intake and normal weight. Three bouts of this reversible obesity seemed to have no lasting effect on their metabolism.

However the degree of obesity, thus induced, varied and at first this was thought to be due to variation in the amount of eating. Later the intake was measured and still the variation in storage response was observed.

Detailed measurements of energy balance were made on six cafeteria fed young animals and on six young controls. In spite of the overfed group taking in 80% more energy than the controls,

the weight gain was only 27% greater than that of the controls. The energy cost of weight gain did however vary considerably as between strains of rat but also to some extent between individuals of the same strain. Rothwell and Stock wrote "..... small differences in genetic and/or environmental background can exert a profound influence on the metabolic response to overfeeding". They saw parallels here with studies in man.

These differences in energy balance could not have been due to extra physical activity on the part of those rats who gained less weight because all the animals were kept in a very restricted space. They could only have been due to DIT and later measurements of oxygen consumption confirmed this.

The experimenters then examined the effect of different sized doses of noradrenaline on cafeteria fed and on control animals. The cafeteria fed group showed a greater sensitivity throughout the range of doses. Sensitivity was assessed from temperature measurements (rectal, interscapular and on the abdomen, just over the liver) using thermocouples.

At this point Rothwell and Stock began to suspect that DIT was linked to non shivering thermogenesis (NST) probably through the activity of brown adipose tissue (BAT).

At 21 days the animals were killed and the interscapular BAT was dissected out. The weight was similar to that found in rats adapted to 5°C (cold adapted rats) but more than twice that in controls. The increase was due to increase in active tissue mass (cf Tulp - page 41) rather than 'excessive lipid deposition'. The basal release of free fatty acid from the BAT was similar in both groups but, when stimulated by noradrenaline, was four times greater in cafeteria fed rats.

It was however felt that other systems were involved as the white adipose tissue also showed greater lipolytic sensitivity to noradrenaline in 'cafeteria' rats. Again the thyroid hormone,  $T_3$ , levels were elevated by 27%.

In overfed human subjects it had also been demonstrated that  $T_3$  levels were elevated.

Rothwell and Stock (23yr old female and 36yr old male) then tried, using infra red thermograms, the effect of oral ephredrine on their skin temperatures and did find significant increases at certain sites i.e. over the nape of the neck, interscapular points and over the sternum. These are known BAT areas.

Previously during 1960s, Stock had taken part in a study of oxygen consumption in subjects who were overeating by 1000 cal per day. Oxygen was used in excess of expectation and weight gain did not explain this. It appeared now that the oxygen was being used to burn off calories as heat.

They concluded - 'Our findings now raise questions as to the advantages of possessing this energetically wasteful tissue'.

#### Reduced thermogenesis in obesity

Nature for 24th May of the same year had carried a letter from Jung, Shetty and James of the Dunn Clinical Nutrition Centre, Addenbrooke's Hospital, Cambridge and their findings were included with those of Rothwell and Stock in the television documentary. Their paper was published in the International Journal of Obesity.

Jung et al mentioned the two components involved in deposition of excess body fat in genetically (ob/ob) obese mice, namely overeating (hyperphagia) and increased metabolic efficiency. They had found in pre-obese and obese ob/ob animals a reduced

thermogenic response to cooling. The obese adults also had a reduced response to noradrenaline infusion and persistent dieting did not change this lack of response.

The letter outlined their experiment with six obese women, aged 40-50yrs with a personal and family history of obesity and seven lean controls of similar age who could eat freely without becoming overweight. They also used an unspecified number of post obese subjects whose weight had been stable for at least 3 mths before the test. All subjects were euthyroid and normo-tensive.

Noradrenaline was infused intravenously in a dose related to ideal body weight (0.1 mg per kg IBW per minute through a brachial vein for 45 minutes). This dose corresponded to that induced by moderately severe exercise.

Before the infusion the subjects rested supine for 30 minutes and then for a further 30 minutes the resting metabolic rate was measured at 1 minute intervals. They were in a fasting condition (twelve hours without food) had been in thermoneutrality ( $27.2^{\circ} - 27.6^{\circ}\text{C}$ ) for one hour and wore identical clothing. The metabolic rate was monitored throughout the 45 minutes of the infusion. Blood was removed for assay from the non-infused arm.

There was with all subjects following infusion an immediate increase in resting metabolic rate (RMR) but the lean increased by 21.2% and both the other groups by only 9.6%. The plasma noradrenaline rises were similar in all three groups throughout.

In actual fact the RMR of the obese group had been greater than that of the other two groups before the infusion. (This is not particularly surprising and probably reflects their increased lean body mass). Davies (1978) had already reported elevated



metabolic rates in obesity and certainly any movement by an obese person is now known to cost more energy than a comparable movement by a person of normal weight, although some observers maintain that in general the obese move less (Jung and James 1980). The RMR of the obese group remained above the level of the other two groups after the infusion but, as has been stated, the percentage increase was considerably less than that of the lean. In 1981 the editor of the British Medical Journal (Clinical Research) commented on the higher metabolic rates of the obese which nevertheless showed less increase than did those of the lean after 50 g. of glucose).

Jung et al suggested that there was indication of a greater lipolytic response to noradrenaline in the obese and therefore defective heat production could not be explained by subnormal lipolysis. Suspicion rested upon a defective thermogenic system as the cause of their overweight. They concluded - 'Our studies suggest that a similar (to the ob/ob mice) mechanism may be involved in adult human subjects as brown fat has been identified even in elderly men and women'.

Tulp (1981), in his paper on experimental overnutrition in rats, described BAT as follows - 'a high concentration of cytochromes impart a brownish colour - distinguished from white adipocytes by a larger more centrally located nucleus, surrounded by coarsely granular cytoplasm and numerous small, lipid locules 16-30 microns in diameter - abundant number of spherical, densely packed mitochondria'.

It was not felt that the defect in these women was connected with their previous energy intake. Two of the obese had been deliberately overfed by 40 cal per kg LBW per day for 7 days

before the test and their response to noradrenaline was not different from that of the other four obese subjects.

In 1979 the editor of the Lancet commented that the connection between obesity and a defective diet - induced thermogenesis, in brown fat, might well be hard to prove but the Dunn Clinic is pursuing its researches along this line. In 1981 James from the clinic reported that postprandial thermogenesis is reduced in familial obesity. Although he admitted that this could be due to altered 'substrate storage pathways' as well as reduced induction of brown adipose tissue.

A Canadian researcher Bukowiecki in 1982 reported on the use of ephredrine as a potential slimming drug, stating that -

'ephredrine mimics the calorogenic action of norepinephrine by directly stimulating brown adipose respiration via -  $\beta$ -adrenoreceptors.

F. FAMINE/FEAST

Obesity and the Development of the Diffuse Neuro endocrine System

Margules of the Dept. of Psychology, Philadelphia was interviewed concerning his theory on a BBC Radio 4 Science programme in 1980.

Early in one of his papers (1980) is the following:-

"Much can be learned from the obese themselves who describe a stressful bone-wrenching hunger upon abstinence from favoured foods". He mentions the "addictive-like" attachments to 'palative' foods and then speculates about the possible involvement of opioid-like peptides in energy balance. Food in the stomach stimulates the production of insulin which facilitates the passage of glucose, fatty and amino acids into the cells. So overeating stimulates over production of insulin which leads to overstorage. Sometimes however, without eating, there can be a breakdown by glucocorticoids and glucagon of the lean body mass and insulin again here is involved in storage. Margules formed the theory that opioid-like peptides stimulated the production of insulin even in the absence of gut signals. He then looked at Cushing's Syndrome where there is over production in two systems - the pituitary ACTH/adrenocortical glucocorticoid axis and the pituitary  $\beta$ -endorphin/pancreatic insulin axis. He speculated that Cushing's Syndrome was an exaggeration of a possibly normal rhythm. Or it could be said that overweight, particularly that of middle age (where there is normally 38% of adipose tissue at 55 yrs as compared with 25% at 25 yrs) could be thought of as a very mild version of Cushing's Syndrome.

Margules examined the physiology and metabolism of the genetically obese strain of mouse (ob/ob) and the rat that was obese from over eating (fa/fa), particularly the effects of

$\beta$ -endorphin and the naloxone that reversed its action. He eventually advanced the theory that every cell in man and probably in all species will have opioid receptors, even an amoeba where pinocytosis can be inhibited by opioid like substances and this reversed by naloxone. The opioid producer cells belong to a diffuse endocrine system. There are forty different types of cell that can secrete these substances but all have their origin in the embryonic digestive tube. They are known as the APUD cells and he felt that they were involved in 'arousal' too by inhibition of opioid peptide release

stimulation of 'endoloxin' release

an inhibition of biogenic amino uptake

a stimulation of biogenic amino release

Endoloxin was the name he gave to a naturally occurring 'naloxone' - like substance. He had found that naloxone injected in a hibernating hamster increased its heartbeat thus causing it to come out of its hibernating state.

Putting his speculations and experimentation together he formulated the famine/feast hypothesis,  $\beta$ -endorphin conveys a message of expected food shortage causing pre-famine feeding which has a distinctive quality being associated with hyperinsulinism. The endorphinergic system accomplishes the necessary preparation :-

lethargy

passivity and skeletal muscle relaxation

attenuation of the arousal capacity of pain, cold,

asphyxiation, oxygen lack and the emotions of

fear and rage

lower set point for core temperature

elevation of set point for carbon dioxide in the blood

maximum storage of nutrients, water and minerals  
stimulation of thirst and appetite  
conservation of sodium and carbohydrates  
reduction in sexual urge

$\beta$ -endorphin is one of the peptides which have a half life sufficiently long for them to reach distant sites in the body.

The 'endoloxin' substance gives a message of expected surplus. Food, water and salt appetite is inhibited and there is an elevation of core temperature. Calcitonin could be involved in the arousal mechanism. It is known to stimulate urinary secretion which  $\beta$ -endorphin inhibits. The shivering known as "wet dog shakes" (thought to be a toxic aberration) which is seen in patients with withdrawal symptoms following the stopping of an opioid drug could be the experiencing of the physiological reaction that was originally developed to arouse animals rapidly from hibernation.

#### IV INVESTIGATING THE 'TRIGGER' MECHANISM

Margules has cited the hormone calcitonin as a possible 'arousal' agent and  $\beta$ -endorphin, an indogenous opioid produced in the brain and in the pituitary gland, as the substance which, without a stimulus from overeating prompts the storage of fat. If ingested substances do in fact act as 'triggers' then, supposing Margules theory to be correct, they should either encourage or discourage the production of either calcitonin on the one hand or  $\beta$ -endorphin on the other.

#### Arousal

##### Calcium, Calcitonin and Parathyroid Hormone (PTH)

Calcitonin, a lipophilic single chain polypeptide of 32 amino acids, was first postulated by Copp et al (1962) as a hormone which lowered the plasma calcium. It is secreted by the parafollicular cells of the thyroid gland in response to hypercalcaemia and it is now quite established that it inhibits the resorption of calcium from bone, a process which is, in turn, induced by parathyroid hormone. Calcitonin and parathyroid hormone together thus constitute a control mechanism for plasma calcium. Jennings in 'Vitamins in Endocrine Metabolism (1970), suggests that PTH effects the coarse reaction and calcitonin the rapid, fine adjustment in the other direction.

Ionised calcium in the plasma is the only stimulus, it is thought, for the secretion of parathyroid hormone and this secretion ceases when the plasma calcium exceeds 3.0 m.mol/litre. Calcitonin production is stimulated by the serum calcium level starting at about 2.0 m.mol/litre and also by gastrin,

cholecystokinin - pancreozymin and glucagon, all of which are secreted directly or indirectly in response to food in the gut.

#### The Involvement of Calciferol (Vitamin D)

Intricately involved, however with calcitonin/PTH homeostatic control is the vitamin, calciferol. The physiological effects of this vitamin arise mainly from its metabolite, 1, 25 - dihydroxychole calciferol (1,25 - DHHC) which is produced when the plasma calcium is low. The low calcium level will of course have stimulated the secretion of PTH and this actually appears to stimulate the production of the metabolite but low levels of plasma phosphate and the presence of prolactin and growth hormone also have an effect. Then 1, 25 - DHHC is definitely known to act in the small intestine causing active absorption of calcium but may have other metabolic significance including a role in reabsorption in the kidney tubules. When the plasma calcium level is high, 24, 25 - di hydroxycholecalciferol is produced from the vitamin instead and this metabolite has little influence on calcium absorption. It is not known whether it influences reabsorption in the kidney in man.

Calcitonin exerts its action unaffected by the actual presence or absence of either PTH or 1,25 - DHHC, although of course their effects influence its secretion. PTH and vitamin D are however much more dependent one upon the other and all of these very complicated interactions are also involved with phosphorous and possibly even magnesium levels. (Papapoulas et al 1980)

#### Calcium Homeostasis

Ionised plasma calcium is of great importance for the normal functioning of muscles and nerves and is intimately involved

in a great number of body processes. Douglas wrote in 1968 in *Hypophysiotropic Hormones of the Hypothalamus* (Edit Meites) - 'On reviewing the evidence one is astonished by the diversity of cells, whose secretory activity is critically dependent upon calcium, and by the variety of stimuli and secretions involved'. From many sources in the literature it is clear that ionised calcium is closely involved in many functions.

It is not therefore surprising that its level is kept constant within narrow limits inspite of its continuous absorption, reabsorption or resorption, secretion or excretion. The dietary variation is well buffered and although a daily intake of 1000 mg is average, normal levels in the bones and in the plasma can be maintained with an intake as low as 100 mg. There must however be a sufficiency (about 2.5 mg daily for adults and perhaps four times as much for infants) of Vitamin D, present either from dietary intake or from the action of UV light on the provitamin in the skin (or from stores in adipose tissue and in muscle). Although calcium deficiency due to dietary insufficiency is rare, and normally dietary excess in no way effects metabolism, the unrequired material passing out in the faeces, the possibility of lack of absorption due to insufficient Vitamin D in the diet and/or a lack of sunlight could cause hypocalcaemia. Substances such as phytic acid (in unfermented wheat bran) and oxalic acid (in rhubarb and spinach in very small amounts) block calcium absorption by forming insoluble calcium compounds and could alter the plasma level to some extent.

[Ole Lederballe Pedersen (1981 - in *Acta Pharmacol Toxicol*) (Copenh) - 49 Suppl 2 : - 31) mentions Tiapamil - a new calcium antagonist - and Verapamil and nifedipine. Rats with hypertension are more dependent upon extra cellular calcium for contractile activation



of aortic smooth muscle (at least the tissue appears to be in vitro) and Pederson proposes a system of calcium transport across membranes. The supplement is devoted to Calcium Blockade as a therapeutic principle in arterial hypertension].

The amount of absorption of Vitamin D from the intestine depends upon the presence of bile and also upon a favourable pH (Jennings 1970) but gross hypocalcaemia which leads to hyper excitability, then tetany and eventually spasm or seizure is very uncommon nowadays in Western Society. Excessive intake of Vitamin D can cause hypercalcaemia with chronic deposition of calcium in soft tissues and/or more acutely, thirst, tiredness and eventually coma but this also is not frequently encountered.

It is however possible that phytic or oxalic acids could cause a small unpathogenic temporary lowering of plasma calcium (the PTH secretion is much slower than that of calcitonin) while an excess of Vitamin D could cause a slight hypercalcaemia which, by stimulating calcitonin might thus effect arousal. For damage caused by excess Vitamin D to be lethal it is thought that a dose 2000 times the required intake would be needed but an accumulative effect from prolonged ingestion of much smaller amounts is likely. There could perhaps therefore be an accumulative non-pathogenic effect when the intake of Vitamin D, the concentration of which varies seasonally in milk and other foods, increases slightly over a period.

#### GABA

An increase in circulatory calcium causes among other effects an increase in the production of - aminobutyric acid (GABA)

(Hems 1980), a possible central nervous system inhibitory transmitter, that is strongly suspected of increasing appetite (Orosco et al 1981) - (see Related Research).

An increase in plasma calcium, resulting in an increase in calcitonin and hence 'arousal' would at first stimulate appetite (via GABA) and then, as calcitonin reduced the plasma level, the appetite would lessen.

Difficulties arise here however. If an increase in appetite belongs to the 'preparation for famine' state then the economical use of and the storing of excess energy should accompany it and one would also expect the core temperature to drop gradually before the actual 'enduring famine' state is reached. GABA production is however (see Related Research) associated with the energy expensive GABA shunt while B-endorphin, supposedly operative in the famine state, according to Liang-Fu Tseng (1981) causes analgesia but also hyperthermia in rats.

#### The Famine State

##### $\beta$ -endorphin

Most of the research connected with  $\beta$ -endorphin and other opioid peptides is concerned with where in the brain they are secreted, the position of receptor sites, together with in vitro experimentation aimed at identification of their agonist and antagonist enzymes. Liang-Fu Tseng injected rats with  $\beta$ -endorphin intra cerebroventricularly and did find a food intake increase which naloxone blocked. He also found the hyperthermia referred to above. Margules engaged in similar experimentation found that naloxone only reduced eating in obese rats.

There are very few clues as to what circulating substances could trigger the production of  $\beta$ -endorphin other than various statements to the effect that it is calcium dependent and that

it is produced to excess together with adrenocorticotrophic hormone (ACTH) in Cushing's Syndrome but the research done by McKay et al (1981) may be significant. They found that a dose of 200 mg per rat increased food intake in a 30 minute meal by 83%. A larger or a smaller dose had no effect!! Presumably the lower dose was insufficient to activate whilst the higher dose may have stimulated other contra-operative receptors. They suggest that the results indicate that  $\beta$ -endorphin is acting centrally to influence meal size and that the effect is 'not one of generalised arousal'.

#### Discussion

The calcium/calcitonin/PTH/GABA interactions could well operate, wholly or partly the feast/famine cycle and the indigenous opioid may well be involved but the pattern is immensely complex. A number of enzymes not mentioned above agonise or antagonise the activities of these substances and in some cases the molecule itself in over production acts as its own inhibitor. McKay's discovery of the effect of  $\beta$ -endorphin over a very narrow concentration range suggests that it may well be the amount of a substance absorbed rather than the ingestion of a less ubiquitous nutrient or trace element that is critical.

## V THE DIFFICULTY OF 'TYPING' OR ASSESSING INDIVIDUALS

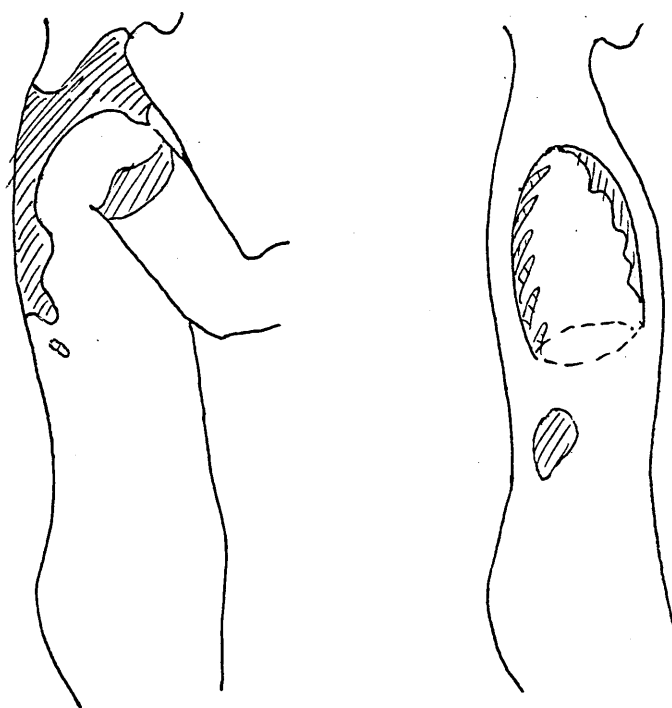
### A. Respiratory Quotient and pH

#### The original Aim

The original aim of this investigation, as indicated in the introduction, was to devise a method of distinguishing biochemical types, particularly having in mind Watson's fast and slow oxidisers. He had, of course, tested blood samples from his subjects and had found the best distinguishing parameter to be pH. It was therefore decided that blood pH should be investigated. Direct blood sampling of a reasonably large number of subjects in a non-clinical situation by a non-medical investigation presents problems, however, and an indirect method was sought. (see NOTE Seven)

B. Measurement of temperature over putative brown fat sites

See Note (Six)



Possible Brown Fat Sites

Fig. I

C. Core Temperature (Pilot Experiment)

Anderson (see Related Research) used sophisticated apparatus to measure temperature. Hancock (see Related Research) suggested rectal or tympanic sites as best for estimation of core temperature but mentioned Bernard (1850) who proposed a pendulum-like oscillation of temperature before settling after overheating. He also commented that site limitation could make for inaccuracy. Shock (1981) recommended the rectal site, urine just after passage or the ear but Fox (1975), in a paper on the Uritemp bottle, actually discredited the rectal site. Bacterial activity could elevate temperature here. His Uritemp bottle measurements tallied with those taken in auditory meatus however.

It was therefore decided that a thermocouple or thermister, used in the ear, was the easiest and most accurate method for estimation of core temperature. However as certain unexpected difficulties were encountered in obtaining suitable equipment, some measurements were taken with an ordinary clinical thermometer gently inserted in the auditory meatus and supported lightly by the subject himself for exactly 5 minutes.

Results

Comparison with contemporary measurements at other sites.

See next page.

TYMPANIC MEMBRANE TEMPERATURE MEASUREMENTS  
COMPARED WITH MEASUREMENTS AT OTHER SITES

74.

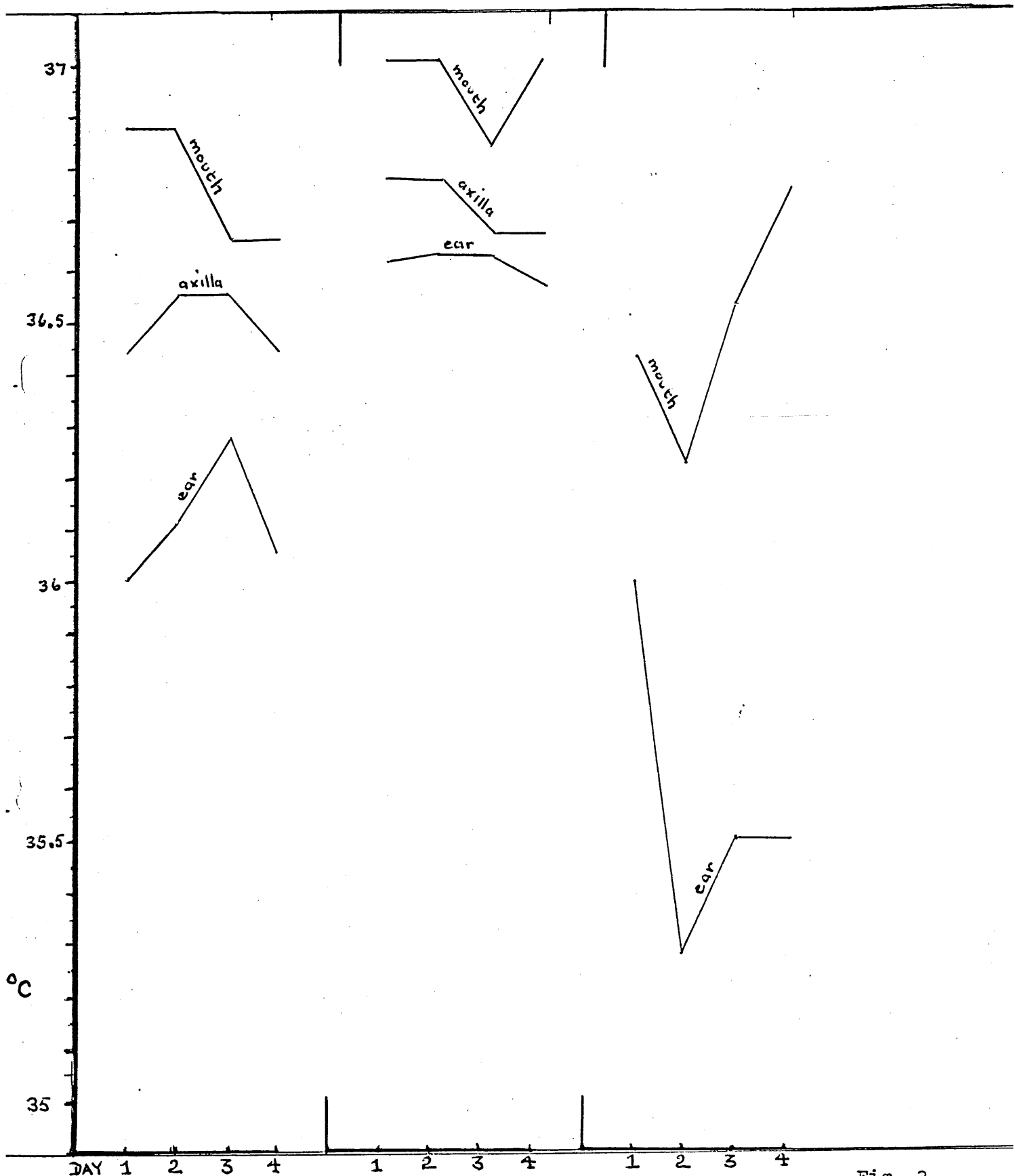


Fig. 2

at 2.30pm  
 SUBJECT 1  
 61yrs  
 moderately  
 overweight,  
 unrestricted diet

at 2.15pm  
 SUBJECT 2  
 75yrs  
 normal weight,  
 unrestricted diet,

at 2.00pm  
 SUBJECT 3  
 58yrs  
 moderately overweight,  
 history of distinctly overw

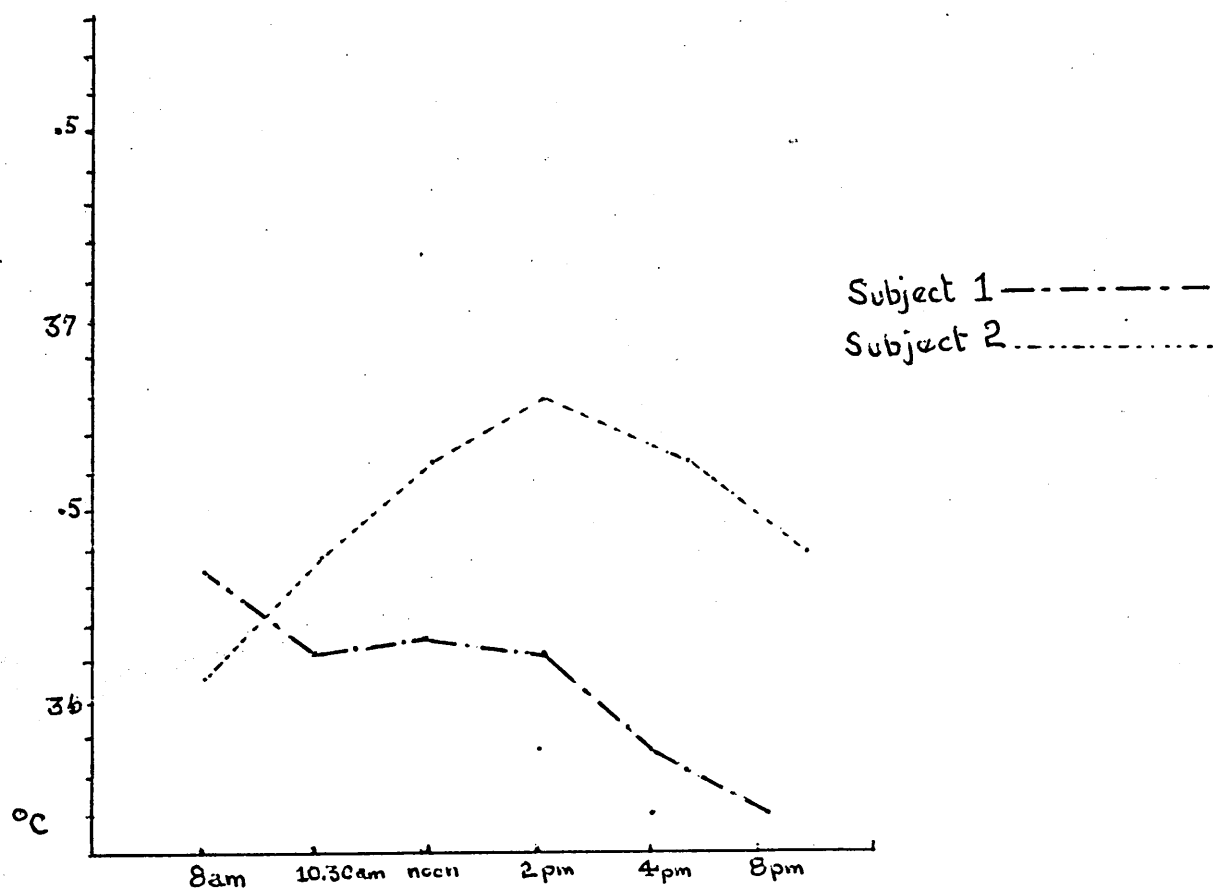
DAILY FLUCTUATIONS (TYMPANIC SITE) - mean of two

Fig. 2a



MEAN OF TWO POST PRANDIAL TYMPANIC MEMBRANE MEASUREMENTS  
 taken 1.30pm-2.30pm on consecutive days CORE TEMPERATURE

76.

	Overweight °C	Age	Sex	Normal or Lean °C
Subject I	36.2	61	F	
" 2		75	M	36.7
" 3	35.4	58	F	
" 4		28	F	36.7
" 5		33	F	36.8
" 6		27	F	36.3
" 7	36.1	38	M	
" 8		34	F	36.6
" 9	36.2	29	F	
" 10		28	M	36.7
" 11	35.8	61	F	
" 12	35.9	66	M	
" 13	36.2	58	F	
Total	251.8			219.8
Mean	35.97( $\bar{x}_1$ )			36.63( $\bar{x}_2$ )

Table 4

For small numbers use combined sample deviation (Swinscow 1976)

Sample deviation 0.4186

$$t = \frac{\bar{x}_2 - \bar{x}_1}{\sqrt{\frac{SD^2}{n_2} + \frac{SD^2}{n_1}}} \quad t = \frac{36.63 - 35.97}{\sqrt{\frac{0.1752}{6} + \frac{0.1752}{7}}}$$

$$= 2.835 \quad 11 \text{ df}$$

$$0.02 > p > 0.01$$

### Conclusion

These results do suggest a correlation between core temperature and weight but the main difficulty of typing by temperature measurement is the variation due to infection. Three of the people, who had agreed to

co-operate, shortly after the measurements had been taken, showed influenza - like symptoms and their statistics were discarded.

Other potential volunteers seemed likely to succumb. It is obviously highly desirable to take measurements frequently over an extended period and this of course makes considerable demands upon the subjects.

## VI THE QUESTIONNAIRE

It is relatively easy to persuade subjects to fill in a questionnaire form particularly if it is undemanding (e.g. requesting ticks rather than sentences) and is not too long. Rosenthal and Rosnow (1984) advise a "funnel sequence" in which questions begin at the most general level and narrow down to the most specific. They suggest that longer questionnaires are more reliable if people will conscientiously answer them but admit that a long questionnaire will often discourage subjects who may fail to co-operate.

However, carefully planned the questionnaire may be there is always the possibility of misreading, misunderstanding or a lack of serious intent on the part of the volunteer who is completing it and surely no scientific conclusions could be drawn from questionnaire derived information alone.

But, as an aid when surveying the field before pursuing a more exact investigation and/or in deciding the precise direction along which to proceed further, it is invaluable.

A social survey guide published by the National Council of Social Service does warn that 'the construction of the questionnaire is perhaps one of the most difficult aspects of any social investigation'. '... there are no rules to determine which of various forms of a question is unequivocally the most suitable and most reliable. This can only be done by trial and error'. Rosenthal and Rosnow also advise piloting before finalising a questionnaire.

Questionnaire A was a generalised research into attitudes and habits connected with food intake.

Questionnaire B was a rough generalised survey of calcium and Vit D intake.

Questionnaire C aimed at keeping up to date, six years later the most interesting aspect of the results of Questionnaire A, namely the concern about overweight which frequently did not correspond with expert assessment of what actually constituted overweight.

#### A. Questionnaire A

This was distributed to sixth formers and students and 186 properly completed replies were received. The sample is analysed below,

Distribution of Sample

	FEMALE	MALE
16-20 yrs	124	2
over 20 yrs	51	9

Table 5a

Distribution of those dissatisfied with their body weight

	FEMALE	MALE
16-20 yrs	73	1
over 20 yrs	28	4

Table 5b

Of these only two, both in the 16-20yrs age group, stated that, although dissatisfied with their weight they were not taking any measures to change it.

According to the Metropolitan Life Assurance figures, of those dissatisfied with their weight, only the following actually were over or underweight.

#### Analysis of the Dissatisfied

	FEMALE	MALE
16-20 yrs	slightly under 3	slightly under 0
	" over 17	" over 0
	moderately over 12	moderately over 0
	very over 1	very over 0
	TOTAL 33	TOTAL 0
over 20 yrs	slightly under 1	slightly under 0
	" over 11	" over 2
	moderately over 4	moderately over 2
	very over 2	very over 0
	TOTAL 18	TOTAL 4

Table 6

slightly = up to 4.5 kg over or under Metropolitan Life Assurance figures.

moderately = more than 4.5 kg but less than 12.7 kg over or under ditto

very (or distinctly) = more than 12.7 kg ditto.

Of those regarding themselves as overweight the mean desired loss of weight was:

#### Weight Loss Desired

	FEMALE	MALE
16-20 yrs	4.0 kg	3.2 kg
over 20 yrs	5.1 kg	5.9 kg

Table 7

Subjects were asked to tick which of the following they would advocate most strongly if asked for advice about weight reduction

- A      more exercise
- B      less food per day
- C      fewer meals
- D      different foods
- E      no 'nibbling' between meals

The following Venn Diagram shows the weight reduction patterns advocated by the female subjects who responded to that question.

(Only two ticked all five methods.)

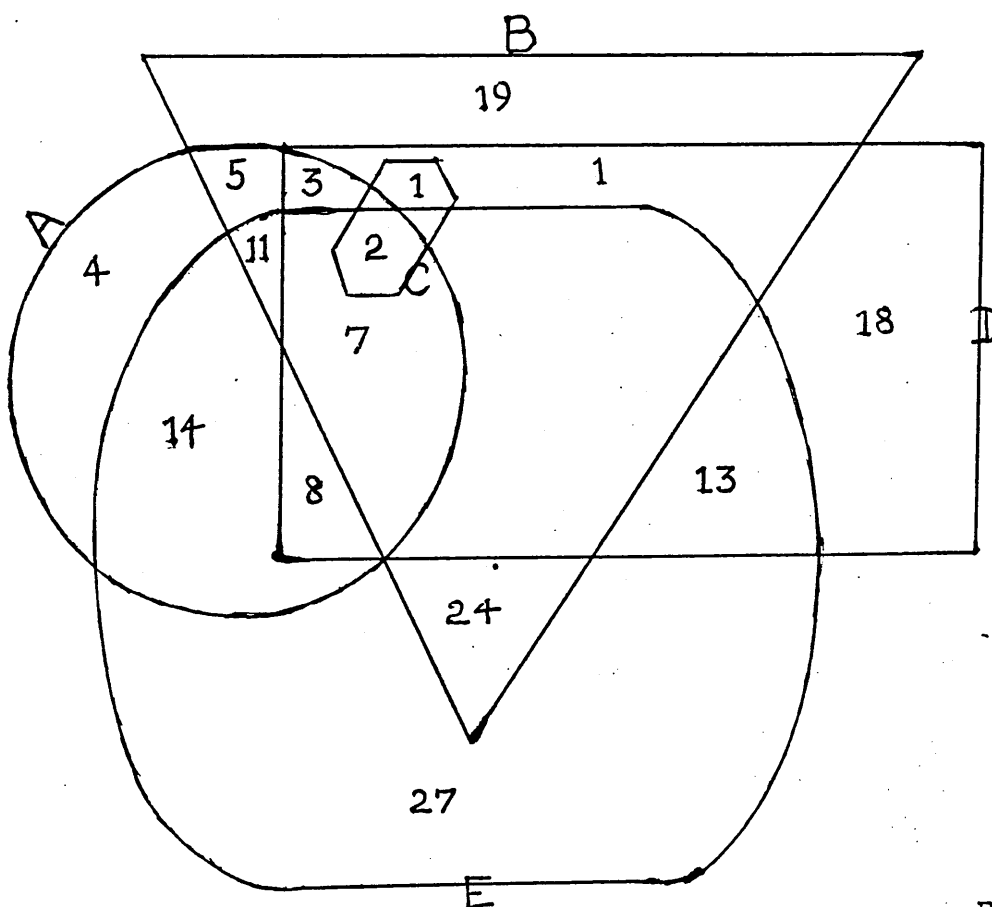


Fig. 3

(The small male sample demonstrated a greater faith in exercise as a slimming aid, 8 out of 11 ticking A and either B or D).

---

Of those who laid faith in one method only (43.3% of the sample)

5.9%	chose	A	
27.9%	chose	B	Females only
26.5%	chose	D	Table 8
39.7%	chose	E	

---

The questions investigating which foods were 'bad' for slimmers and which 'good' for slimmers showed little variation. Fried foods, fatty foods, carbohydrates, chocolate biscuits, cakes, beer, sugary drinks and crisps were 'bad'. Meat, fresh vegetables, fruit, salad and Ryvita were 'good'.

Milk was only mentioned by 8 subjects, 3 regarding it as 'good' for slimmers and 5 as 'bad'.

It could be assumed from the various answers given that at least 84 subjects clearly regarded protein foods as 'good' in this context and carbohydrates as 'bad' but the carbohydrate content of fresh fruit was ignored.

### B. Questionnaire B

If calcium balance were to be operative in the switching mechanism from the 'energy thrifty' to the 'energy expensive' state then could calcium or more likely Vitamin D intake slightly alter the balance? Most of the calcium ingested is expelled in the faeces and it is difficult for a deficiency to occur because of diet alone and a deficiency of Vitamin D is rare in most Western diets of today.

It is not clear from the literature precisely at what level of excess the Vitamin D intake causes damage nor is it known whether a threshold must be reached before potentially dangerous change begins to occur. The change could be gradual and in the early stages form part of the switch over mechanisms. A high intake of the vitamin perhaps together with a high intake of calcium could just conceivably have such an effect.

A questionnaire was designed to show up gross difference in the intake of calcium and Vitamin D. It was hoped that completing the questionnaire would take only a short time and would not demand too much of the subject, who would make his own estimates of his weight, energy output, diet etc.

Forms were offered to the teaching staff at two schools, to a small group of University students, to a small social work agency, to the personnel department at a local brewery and to staff and workers at a small factory. This random (with respect to the physical type) distribution yielded 89 responses.



Below is analysis of the sample.

F = female M = male DO = distinctly overweight

MO = moderately "

SO = slightly "

JR = just right

SU = slightly underweight

DU = distinctly "

	DO	MO	SO	JR	SU	DU
F	5	11	30	10	5	0
M	2	2	12	8	4	0

The dietary intakes of calcium and of the vitamin, from the quantities suggested as average in the questionnaire, were compared (as between different foods) and assigned a ratio (e.g. Calcium - 'a good helping of spinach or kale etc., 3 times per week' = 1, Vitamin D - 'seven eggs per week' = 2). The reduction or increase for 'much less' or 'much more' respectively was considered and it was decided that one third (less or more) was reasonable, except in the case of 'margarine' which has a high Vitamin D additive content and where some later investigation amongst some who had filled in the questionnaire suggested that one sixth was a better estimate.

No significant divergence between calcium intake and vitamin D intake was evident i.e. a high calcium intake was accompanied by a high vitamin D intake and similarly with average and low intakes. Attention was therefore subsequently concentrated on the Vitamin D figures only. In only 5 subjects (1 JR, 2 SO, 1 MO and 1 DO) did a vitamin supplement contribute to the total - "Multivite" containing 400 iu.

Means of the 'ratio values' (Vit. D intake)      Table 10

	DO	MO	SO	JR	SU	DU
M and F	13.5	11.6	14.3	13.5	16.7	-

Interest in the slightly underweight group prompted the selective distribution of questionnaire sheets to 6 apparently lean males, only two of whom actually ticked the 'slightly underweight' box, two ticking 'just right' and the others surprisingly ticking 'slightly overweight'. With these additions, the results were now.

Means of Ratio Values (Revised) Table 11

13.5	11.6	14.8	13.8	16.3	-
n = 7	n = 13	n = 44	n = 20	n = 11	

Vitamin D intake was now described as low  $x \leq 10$  (ratio figure)

average  $10 < x \leq 14$  approx.  
1200 iu per week

Analysis of Results

Table 12

high  $x > 14$ Distinctly Overweight

	LOW	AVERAGE	HIGH
F	0	3	2
M	0	1	1

Just Right

	LOW	AVERAGE	HIGH
F	0	7	3
M	2	6	2

Moderately Overweight

	LOW	AVERAGE	HIGH
F	2	8	1
M	0	0	2

Slightly Underweight

	LOW	AVERAGE	HIGH
F	0	3	2
M	1	1	4

Slightly Overweight

	LOW	AVERAGE	HIGH
F	6	14	8
M	0	6	10

Total Overweight

	LOW	AVERAGE	HIGH
F	8	25	11
M	0	7	13

Total Just Right with Slightly Underweight

	LOW	AVERAGE	HIGH
F	0	10	5
M	3	7	6

Distinctly with Moderate  
Overweight

	LOW	AVERAGE	HIGH
F	2	11	3
M	0	1	3

Slightly Overweight with  
Just Right

	LOW	AVERAGE	HIGH
F	6	21	11
M	2	12	12

WHOLE SAMPLE

	LOW	AVERAGE	HIGH
F	8	35	16
M	3	14	19

TOTAL OVERWEIGHT compared with NOT OVERWEIGHT

Table I3

If the total overweight group (OW) is compared with the not overweight, namely Just Right and Slightly Underweight (NOW) then for FEMALES only

Observed Values (ob)

	OW	NOW	TOTAL
L	8	0	8
A	25	10	35
H	11	5	16
TOTAL	44	15	59

Expected Values (ex)

	OW	NOW	TOTAL
L	5.97	2.03	8.00
A	26.10	8.90	35.00
H	11.93	4.07	16.00
TOTAL	44.00	15.00	59.00

	ob - ex		(ob - ex) <sup>2</sup> / ex	
	OW	NOW	OW	NOW
L	2.03	-2.03	0.690	2.030
A	-1.10	1.10	0.046	0.136
H	-0.93	0.93	0.072	0.213
			0.808	+ 2.379

$$\chi^2 = 3.187 \quad df = 2$$

$$0.3 > p > 0.2$$

The differences could be due to chance alone.

Repeating the test for MALES only      Table 14a

Observed Values

	OW	NOW	TOTAL
L	0	3	3
A	7	7	14
H	13	6	19
TOTAL	20	16	36

Expected Values

	OW	NOW	TOTAL
L	1.67	1.33	3.00
A	7.78	6.22	14.00
H	10.56	8.44	19.00
TOTAL	20.01	15.99	36.00

	ob - ex		(ob - ex) <sup>2</sup> / ex	
	OW	NOW	OW	NOW
L	-1.67	1.67	1.670	2.097
A	-0.78	0.78	0.078	0.098
H	2.44	-2.44	0.564	0.705
			2.312	+ 2.900

$$\chi^2 = 5.212 \quad df = 2$$

$$0.10 > p > 0.05$$

This is still not significant, taking  $\alpha$  as 0.01

For the whole sample, males and females together,  $\chi^2 = 0.261$

$$0.90 > p > 0.80$$

If on the other hand an Extension of the Median Test is applied to the data (Siegel—Nonparametric Statistics for the Behavioural Sciences—P.179) the resulting probability of significance in the LAH grouping comes much closer to  $\alpha$  .

Table 14b

The median is the 'ratio' value 13.5

Observed Values

	OW	NOW
the median value or below	40	20
above the median value	24	11
	64	31

Expected values if there is no connection between LAH values and weight.

Expected Values

	OW	NOW
the median value or below	32	15.5
above the median value	32	15.5
	64	31.0

ob - ex			(ob - ex) <sup>2</sup> / ex	
	OW	NOW	OW	NOW
the median or below	8	4.5	2	1.306
above	-8	-4.5	2	1.306

$$\chi^2 = 6.612 \quad df = 1$$

$$0.02 > p > 0.01$$

### Gender Influence

There is some suspicion of a gender influence on the LAH grouping and a Chi Squared Test showed a probability better than the 5% level.

Observed Values

	L	A	H	TOTAL
F	8	35	16	59
M	3	14	19	36
	11	49	35	95

Table 15

Expected Values

	L	A	H	TOTAL
F	6.83	30.43	21.74	59.00
M	4.17	18.57	13.26	36.00
	11.00	49.00	35.00	95.00

ob - ex				(ob - ex) <sup>2</sup> / ex		
	L	A	H	L	A	H
F	1.17	4.57	-5.74	0.200	0.686	1.516
M	-1.17	-4.57	5.74	0.328	1.125	2.485
				0.528+1.811+4.001		

$$\chi^2 = 6.340 \quad df = 2$$

$$0.05 > p > 0.02$$

Age divided the sample as follows:

91.

UNDER 20

Age

Table 15a

	DO	MO	SO	JR	SU	DU	TOTAL	
F	0	0	1	1	1	-	3	F
M	0	0	0	1	0	-	3	M

33.3% overweight F

20-35

	DO	MO	SO	JR	SU	DU	TOTAL	
F	1	5	16	5	4	-	31	F
M	0	1	7	3	1	-	12	M

71.0% overweight F

66.6% overweight M

35+-50

	DO	MO	SO	JR	SU	DU	TOTAL	
F	3	3	8	4	0	-	18	F
M	2	0	7	3	4	-	16	M

77.7% overweight F

56.3% overweight M

50+-70

F	1	3	3	0	0	-	7	F
M	0	1	2	2	1	-	6	M

100% overweight F

50% overweight M

Over 70

F	0	0	0	0	0	-	0	F
M	0	0	0	1	0	-	1	M



Vit D intake

L LOW

Further Age Analysis

A AVERAGE

Table 15b

H HIGH

20-35

DO MO SO JR SU DU

F	L=0	L=1	L=5	L=0	L=0	-
	A=1	A=4	A=8	A=4	A=3	-
	H=0	H=0	H=3	H=1	H=1	-
M	L=0	L=0	L=0	L=0	L=0	-
	A=0	A=0	A=2	A=2	A=0	-
	H=0	H=1	H=5	H=1	H=1	-

35+-50

F	L=0	L=0	L=0	L=0	L=0	-
	A=2	A=2	A=5	A=2	A=0	-
	H=1	H=1	H=3	H=1	H=0	-
M	L=0	L=0	L=0	L=0	L=1	-
	A=1	A=0	A=4	A=4	A=1	-
	H=1	H=0	H=3	H=0	H=2	-

Looking at the SO group in the 20-25's and comparing female with male:

Female		%	Male		%	Diff
	L	31.25		L	0	31.25
	A	50.00		A	28.57	21.43
	H	18.75		H	71.43	-52.68

The direction of the differences is suggestive.

Opposite polarisation, male from female in the "slightly overweight" group of the 20-35 yr age group, does suggest some sex linkage or hormonal interference which is obscured, perhaps by the menopausal effects, in the 35+ - 50 age group. Numbers are however too small for this to be more than a vague suspicion.

C. Questionnaire C

This was distributed to 31 16 to 18 yr old school girls and requested height, weight, opinion of weight. If dissatisfied with her weight the subject was asked if she were 'doing anything about it' and what she regarded as a desirable weight.

Opinion of Weight

Satisfied	14 average weight 6 slightly under-weight
Not satisfied and 'doing something about it'	1 moderate over wt. 1 slightly over wt. 4 average weight 3 slight under wt.*
Not satisfied but doing nothing about it	1 moderately over wt. 1 average

criteria as before

\*though underweight felt themselves to be overweight.

Table 16

Comparing these results with the earlier survey, using only the females of the 16-20 yr age group,  
Comparison with Earlier Results

Metro Life Ass.	1976	1982
Overweight	24.2%	9.7%
Underweight (including the 'satisfied')	19.3%	29.0%
Dissatisfied because felt themselves overweight	56.4%	35.5%
Of this dissatisfied group those who were not actually overweight (Metro. Life Ins. figures)	57.1%	72.7%
	n = 124	n = 31

Table 17

Percentage of whole sample dissatisfied unnecessarily because of imagined overweight

1976

32.2%

1982

25.8%

## VII CONCLUSION

This study leaves no doubt concerning the complexity of the relationship between food intake and body weight. The nature of the food, including perhaps very small traces of substances that it contains, the state of the individual at any one time, the inherited characteristics of the individual concerned all play their part in determining the amount of adipose tissue laid down.

Much is known about the development of storage tissue and there are strong indications as to which hormones influence the storage process.

Measurement of the amount of fat possessed by an individual is not yet exact nor, when energy expenditure is being considered, is core temperature very easily determined.

The relationship between obesity and disease is far from clear, although many would assume a close connection.

The anxiety associated with weight reduction programmes is worrying and in general, inspite of much effort and a multiplicity of research schemes, the problem of overweight in Western affluent society has by no means been solved.

Research into the literature certainly revealed a need for more large scale, co-ordinated research schemes, perhaps starting with one very large survey from which a number of teams followed up particular interests in a variety of ways but with regular "cross-fertilisation". From all this might spring several experiments, including some longitudinal studies.

The rather scanty statistics obtained from the temperature pilot study certainly suggests that the overweight might well have a lower core temperature.

Questionnaire investigations need very sensitive evaluation and statistical analysis can be misleading. With regard to calcium and vitamin D consumption and its link with body fat, a group of no fewer than thirty each, males and females aged 25-30 years and known to be slightly overweight (Metropolitan Life Assurance figures) presenting a two week typical diet record would be an interesting follow up, although as mentioned elsewhere, the self recording of diet by all but the most dedicated researches leaves much to be desired. Questionnaires A and C revealed the considerable degree of anxiety about weight felt by young females in general.

Work with human subjects has distinctive difficulties, which no doubt explains the preference of many workers for laboratory animals,

and often needs to be extended over a long period to obtain patterns rather than isolated measurements, any one of which may be distorted by a great number of variables. This need for extended examination does of course raise serious but not insurmountable problems of its own. Co-operation of subjects with diet experiments is even harder to achieve if the aim involves a high degree of accuracy. It is not easy for subjects, especially those without a scientific bent, to appreciate that the truth about intake is more valuable than that they should have appeared to have adhered strictly to the suggested diet. The search for less accurate trends may be more productive, these to be checked later using a few very dedicated, well monitored volunteers. The sensible use of human subjects is itself a valid and fascinating area for research.

The last few decades have seen considerable change in the biosphere, largely as a result of man's activity. 'Pollution' has changed the air we breathe, different methods of food production have changed the food we eat, we wear different clothes and often live in warmer surroundings. There are anti-biotic drugs, more efficient disinfectants and more travel, all of which have changed the microbe population in one way or another. The metabolic systems evolved over millenia must be under stress.

If there is indeed an energy expensive state that can be exploited to reduce obesity then experimenting with diet change may well eventually release the trigger and careful recording could be valuable although probably only for that particular subject. But man evolved to a state of affairs where seasonal change was vital and various rhythms must still be important in his body functioning. Much in our civilisation reduces the effect of seasonal temperature change and seasonal food

availability and some recording of seasonal custom in different populations together with assessment of seasonal consciousness in a variety of individuals might well be relevant (See Note ~~Four~~ Four). The ability to 'type' individuals with respect to their homeostatic control of energy storage, whether it arises from genetic difference or from their present 'state', would be a helpful short cut in any large scale therapy.

Undoubtedly the desirable amount of energy to be stored by a person varies from time to time (and at any one time between one individual and another). Possibly we disregard the need for cyclic rhythms at our peril.

Each person is, of course, genetically unique and will, in his lifetime, for the most part, trace a unique pattern of contact with the world outside himself. He will eat a diet which is a combination of

what he fancies

what he can get hold of

and what he thinks he should eat

This last component is itself a mixture of childhood indoctrination (truth and myth), superstition, hearsay, current scientific or medical pronouncements and past personal experience of well-being or suffering following the ingestion of certain foods.

Sensitively derived findings from valid research can help but, in the long run, if the caption on Watson's book, namely 'eat your way to better mental and physical health' is true then it may rest very largely with the individual to work out his own personal solution.

NOTES



## IX NOTES

### NOTE One

Do similar manifestations of disorder necessarily demand similar remedies? Allopathic medicine consists very largely of specific procedures and specific drugs applied after diagnosis of recognisable disease states. Understanding the patient is necessary but only because his individual idiosyncrasy could confuse diagnosis and his history could contra indicate certain drugs etc. The homeopathic approach matches a patient's detailed symptoms to the disorders caused by certain poisons and prescribes that same poison in the minimum dose but it also takes into account individual types. Many of these were described by Hahneman (Homeopathic Materia Medica Para 17) and included accounts of physical appearance, emotional tendencies, mental states.

e.g. 'Pulsatilla - Especially active in persons of a fair, mild type who have marked good humour when well but are easily depressed when ill. It is also specially suited to those who, though fat, cannot take rich fat foods - Disposition - changeableness of symptoms, of moods. Inclined to tears when ill. Uneasiness about affairs and health (Materia Medica in Miniature - Nelson).

Theoretically if the patients drug type can be discovered, this same poison in homeopathic dilution should be of benefit whatever actual symptoms he is presenting and the theory is supported by an abundance of evidence in homeopathic literature. It is acknowledged that the healing mechanism is quite unknown. It would seem that the biochemical process harmonised as a result of these trace substances, although in the case of the higher

potencies (dilutions) there is not even as much as a chemical trace!

In a report of the Proceedings of the 3rd International Pharmacological Meeting held at Sao Paulo to discuss 'Mechanisms of drug toxicity' in 1966, a paper by Brodie of the National Heart Institute, Maryland, contains the following:

'Many investigators do not realise that a common cause of toxic reactions in man arises from 'overdosage' because of person-to-person variability in rates of drug metabolism; the same daily dose of a drug may cure, cause severe toxicity or have no effect whatsoever..... In contrast (to those concerned with polar drugs) researchers concerned with psychotherapeutic and other liposoluble drugs are aware of wide divergences in drug response'.

#### NOTE Two

The role of 'cold' is difficult. Presumably it could be argued that 'cold stimulates the arousal mechanism rather than the reverse so that the organism can maintain its temperature in cold ambient conditions. But of course in temperate regions in primitive societies 'cold' would herald the time of food shortage.

In some tropical or semi tropical climes seasonal variation is not marked and there is no particular time of food shortage but others have a cycle involving drought, which is often also a period of greatest heat. Arctic conditions pose yet another question. Is brown fat active all the year round in people acclimatised to life within the arctic circle? Investigations of this sort have not yet been described. Berchtold et (1981) found an above average tendency to overweight amongst females of both Asiatic and West Indian origin living in West Germany

but with the Asiatics the tendency was much more pronounced among the elderly.

### NOTE Three

In his book "Dangerous Plants (1977) Tampion\* states '..... even a particular species of plant will differ in the amount of poison it contains..... may vary during the growing season..... in some regular way during the growth cycle of the plant or, even worse, vary according to the prevailing weather conditions during the season. We often find that different strains of the same species may have widely different amounts of poisonous substance in them even when grown under identical conditions'. This surely will also apply to substances not strictly poisonous.

If animals experience cycles, plants vary in chemical content and the weather shows fluctuation then the ability of an organism to adapt to prevailing conditions must be exceedingly advantageous.

Instances of homeostatic adjustments operating via a food substance are infrequent in the literature although this may not necessarily suggest that their occurrence is infrequent (Wurtman in Nutrition and the Brain, Vol.1). Lee (1968) does however give an account of the Californian quails and this is quoted by Gaulin and Konner, writing in the same volume on the Natural Diet of Primates.

In dry years the quails are forced by scarcity to eat plants containing phyto estrogens which inhibit egg production but in wet years their food contains little or no phytoestrogen and there is prolific egg laying.

### NOTE Four

If one considers life in a temperate clime such as Great Britain in primitive times, what could be the pattern of the annual cycle?

\* Tampion J (1977) Dangerous Plants. David & Charles

Summer plant growth would fatten game, supply fresh leaves and roots thus producing a time of plenty. Warmer weather would demand less thermogenesis. Autumn fruits, including uncultivated grain, which could have been stored, together with fattened game would extend the plenty period until near to the mid winter solstice. Soon after this the severe cold would favour arousal with reactivation of the brown fat. Hunting would demand greater mental agility and more physical activity. Food would be very scarce and the stored energy in the white adipose tissue would gradually be drawn upon. Libido would increase so that, although Man has no especial fertility season, spring would in fact have been the main mating season. Eggs would become plentiful, also plant shoots would be available.

If one postulates the four states therefore

Arousal would be-mid January

Adjustment to plenty (?) - mid April

Famine preparation - mid July

Adjustment to famine - mid December

The terms 'plenty' and 'famine' no longer fit as precisely as in Margules' original generalisation.

A number of difficulties present themselves. The summer is not normally considered to be the period when appetite is at its keenest and increased appetite together with a more economical biochemistry are characteristic of the famine preparation state. Also what in the mid January lean diet could have stimulated arousal?

• • • • •  
It would seem that little of the above is actually relevant since Gaulin & Konner (1968) write that 'Man adapted to very different conditions from those that have obtained in different eco niches at different times since, including conditions to-day. The

The important thing is what people ate during the hunting-gathering era, which lasted for 99% of generations of the genus homo. Moreover Lee declares that most of human evolution took place in the lower latitudes. The Kung San or Bushmen of the Kalahari Desert of Botswana probably give the nearest parallel to the lifestyle of our earliest ancestors and their diet includes 85 wild plant species, nine of them constituting 75% of their vegetable intake which is itself about 70% of the total diet. Three of the nine have been analysed.

Mangongo (nut & fruit)

tsi bean

Sa tuber

and these alone contain most of what would now be regarded as essential nutrients. The mangongo is almost the staple food and is available all the year through but at certain times the Bushmen have to travel further in order to obtain supplies.

#### NOTE Five

Few recently produced inorganic chemistry books give more than a passing mention of carbonic acid solutions.

Partington\* (General and Organic Chemistry) states that carbonic acid dissolves in its own volume of water at 15°C. At a pressure greater than 4 or 5 atmospheres solubility increases more slowly than the pressure. At 25°C the dissociation constants are as follows:-

$$K_1 = \frac{[H^+][HCO_3^-]}{[total CO_2]} = 4.3 \times 10^{-7}$$

\* Partington J R General & Organic Chemistry (2nd edition 1958)  
McMillan

$$K_2 = \frac{[H^+][CO_3^{2-}]}{[HCO_3^-]} = 4.7 \times 10^{-11}$$

'Probably', he states, 'only 1% of dissolved CO<sub>2</sub> is hydrated to carbonic acid?

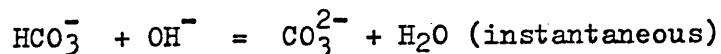
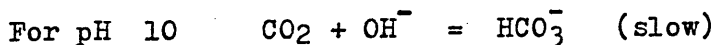
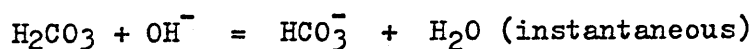
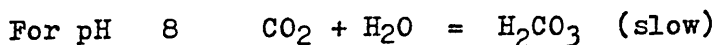
He quotes McBain (J.C.S. 1912 101 814) and others, the latest being Urey (J.A.C.S. 1940 62) who mention that CO<sub>2</sub> + H<sub>2</sub>O ⇌ H<sub>2</sub>CO<sub>3</sub> requires time and neutralisation with alkali is 'not instantaneous'.

Cotton and Wilkinson <sup>\*</sup> (Advanced Inorganic Chemistry) give the dissociation constants as K<sub>1</sub> = 4.16 × 10<sup>-7</sup>

K<sub>2</sub> = 4.84 × 10<sup>-11</sup> and state that the true activity (because the greater part of the dissolved CO<sub>2</sub> is not H<sub>2</sub>CO<sub>3</sub> but a loose hydration only) is 2 × 10<sup>-4</sup>

They state that the rate of dissociation is very slow and 'this slowness is of great importance physiologically and in biological, analytical and industrial chemistry'.

The neutralisation of CO<sub>2</sub> has two



For pH 8 to 10 the comment is merely 'both mechanisms are important'.

L & M Fieser (1956) state that "Carbonic acid is a gem-diol and exists as such to only a slight extent in aqueous solution in equilibrium with carbon dioxide and water."

#### NOTE Six

The original meter designed to measure oxygen and carbon dioxide concentrations measured approximately 26 cm x 18 cm x 10 cm and

\* Cotton F A & G Wilkinson Advanced Inorganic Chemistry. 3rd edition 1972 Inter Science

incorporated transistors into its circuitry. Later, the silicon chip having become readily available, a new meter was devised measuring 15 cm x 8 cm x 4 cm but, owing to the difficulties with the carbonic acid solutions, this was not standardised for pH measurement.

Some attempt was however made to use this meter for measurement of heat emitted through the skin over brown fat sites. Two pairs of copper discs, in each case one to lie on the surface of the skin and one held a few millimetres above the surface, were connected so that the meter registered the difference between the pair differences. The idea was that one pair should be placed over a brown fat site and the other a small distance away but supposedly clear of the brown fat.

Considerable testing, using membranes stretched over vessels containing water at known temperatures to simulate the human body, resulted in a suspicion that the circuitry of the meter was incorrect and it was returned to the laboratory for revision.

NOTE SevenRespiratory Quotient (RQ)

Respiratory quotient is defined as the volume of carbon dioxide, produced in an oxidation, divided by the volume of oxygen used. The RQ for the oxidation of carbohydrate is 1.0, for human fat 0.72 and for protein about 0.80. The term is often employed however to describe the total effect of all biochemical reactions in an individual and at any one time can be calculated from the carbon dioxide content of exhaled air, divided by the volume of oxygen extracted from ambient air.

The actual relationship between the carbon dioxide addition and the oxygen extraction effects in an exhaled sample is exceedingly complex and dependent upon a number of variables (West<sup>\*</sup> in Ventilation/Blood flow and Gas Exchange, reprinted 1972) but, in a normal, healthy individual, analysis of an end tidal sample does yield a respiratory quotient which closely approximates

\* West J B(1965) Ventillation/blood flow and gas exchange.  
Blackwell Scientific Publications



to alveolar concentrations and thus to the chemical activity in the blood.

For the most part RQ calculated from analysis of alveolar air is in the range 0.71 - 1.0 but the transformation of carbohydrate to fat results in the production of carbon dioxide, although oxygen is not used, and reverse results arise from the reverse transformation. RQs outside this range are therefore possible if lean subjects are fed large amounts of carbohydrates or obese subjects are made to fast. Assuming ordinary nutrition, a mixed diet usually resulting in an RQ of about 0.85, the expectation of a slightly higher average figure for Watson's 'fast oxidisers' and a slightly lower for his 'slow oxidisers' is reasonable.

#### Alveolar pCO<sub>2</sub>

Henderson in 1908 published work on the physical significance of carbonic acid, relating the product of the hydrogen ion and bicarbonate concentrations to the concentration of dissolved carbon dioxide and in 1916 Hasselbach introduced the logarithmic expression. The equation now known as the Henderson-Hasselbach equation (one version being  $\text{pH} = \text{pK} + \log \frac{(\text{HCO}_3^-)}{\text{L} \cdot \text{pCO}_2}$  where L =

Solubility coefficient of dissolved CO<sub>2</sub>) arose from their work and was originally used to calculate plasma pH from gasometrically measured alveolar pCO<sub>2</sub>, before pH electrodes had been developed.

Refined work by Siggaard-Anderson\* (The Acid-Base Status of the Blood 1974) relates, in the normal physiological blood pH region, a pCO<sub>2</sub> change of 0.1% to a pH change of 0.02.

\* Siggaard-Anderson O (1963) The Acid-Base Status of the Blood. reprint 1974 Munksgaard

### Original Plan

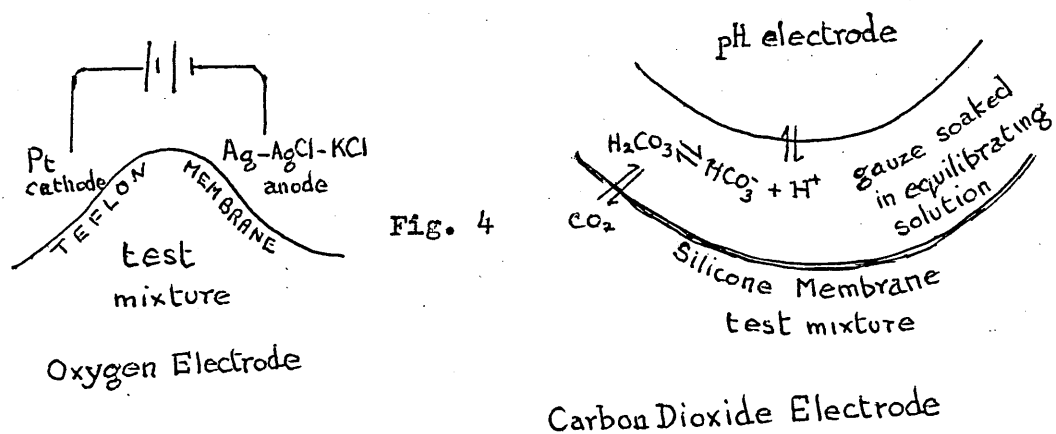
It was therefore decided to test  $O_2$  and  $CO_2$  concentrations in exhaled air (an accuracy of at least 0.1% being necessary) to within  $\pm 0.05\%$  if possible.

### Practical Work

A portable meter (see Note six) was devised, capable of registering by means of one circuit, the change in an oxygen electrode and, by means of an alternative circuit, the change in a carbon dioxide electrode in each case resulting from the trapping in the manifold, into which both electrodes were inserted, of an end sample of exhaled air. A dial registered gross change and had a  $\times 10$  alternative for fine measurement. In order to standardise this apparatus, cylinders of standard nitrogen,  $CO_2$  and  $O_2$  mixtures were obtained.

### Difficulties

- (1) At no time were results consistent and the circuitry was completely revised twice. Eventually the meter underwent laboratory tests which established its accuracy.
- (2) Suspicion then fell upon the electrodes, especially the  $CO_2$  electrode which gave a very variable response.



The silicone membrane certainly showed a tendency to form small holes and several different types were tried.

(3) As part of the experimentation with the CO<sub>2</sub> electrode, the membrane was removed and the resulting pH electrode was placed in bicarbonate solutions of various concentrations. Standard O<sub>2</sub>/CO<sub>2</sub> mixtures were bubbled through and the pH of the solutions was read on a variety of pH meters, inconsistency being noticeable even here. Nevertheless reaction, though insufficiently predictable for the accuracy required, was more within the expected range and it was concluded that

- (i) measurement with electrodes in a gaseous medium needed a lengthy registering period and
- (ii) the design of this particular manifold was imperfect, the water vapour and leakage making for further inaccuracy, particularly in view of the time required for stabilising.

(4) The use of carbonic anhydrase, which in vivo is thought to hasten the equilibration of carbon dioxide with water, was found to enhance the reaction slightly in weak bicarbonate solutions but did not shorten the period required for stabilisation.

(5) Further tests with the pH electrode in bicarbonate, saturated with standard O<sub>2</sub>/CO<sub>2</sub> mixtures, were done with colour indicators and here the rapidity of colour change showed clearly the extreme instability of the carbon acid. Change was such that an accurate dial reading was impossible. A needle recorder was contemplated but even the most finely tuned meter requires a few seconds to stabilise and it was concluded that accuracy

with bicarbonate solutions in an open system was not practicable. It was therefore decided to devise a closed system, as shown below:

Closed System Plan

Fig. 5

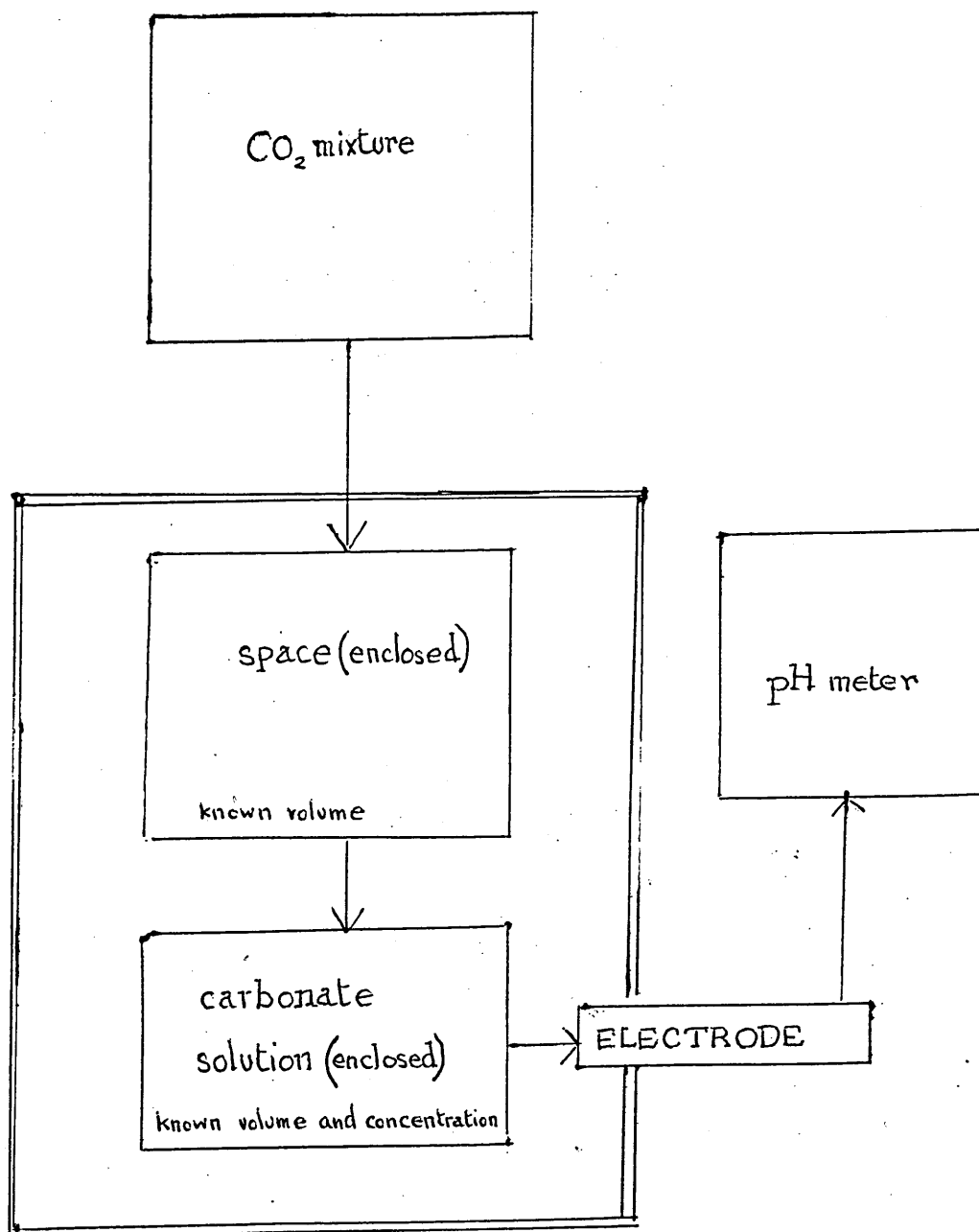
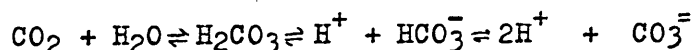


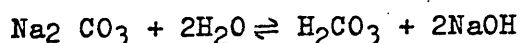
Diagram of flask is on page 112

(6) Various concentrations of sodium carbonate were prepared and tested. In each case 2 ml was placed in the bulb at the base and this just covered the bulb of the electrode. The taps were opened and either the standard gas was allowed to flow through for 40 seconds or a subject exhaled through and, in the latter case, the taps were closed as he indicated that he was practically at the end of his exhalation, a tidal end sample thus being trapped. The apparatus was then shaken every 2 minutes for an 8 minute period, after which the carbonate was apparently saturated and in equilibrium with the gas.

The flask had a capacity of exactly 130 ml, excluding the space filled by the electrode. It was theoretically possible therefore to use the pH change in the solution to calculate the percentage of carbon dioxide in the air sample. Basically the relevant reactions centre around:



However the presence of sodium carbonate involves



$2\text{NaHCO}_3 \rightleftharpoons \text{Na}_2\text{CO}_3 + \text{H}_2\text{O} + \text{CO}_2$  depending upon concentration and other factors.

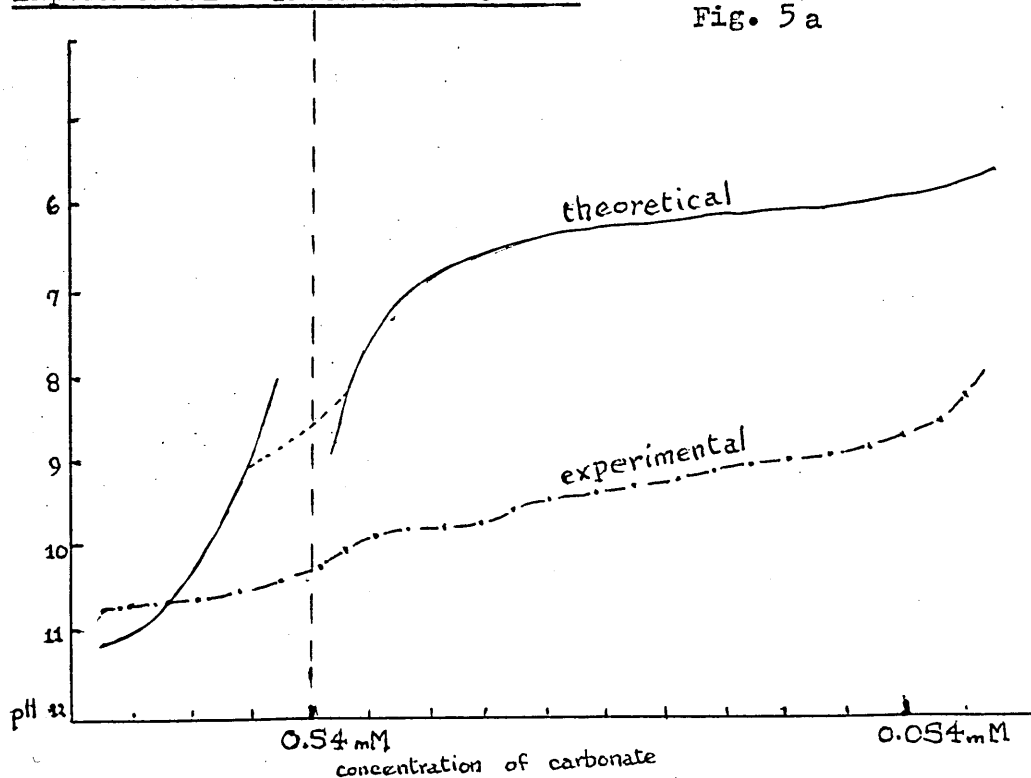
Siggaard-Anderson suggested  $\text{NaCO}_3^- \rightleftharpoons \text{Na} + \text{CO}_3^{2-}$  in 1962 but Maas queried this in 1967 although a similar reaction with calcium bicarbonate was demonstrated by Pederson in 1971.

The Henderson-Hasselbach equation was used in the applicable range and a theoretical curve was drawn.

7. The experimental curve by no means approximated to the theoretical curve.

Experimental & Theoretical Curves

Fig. 5 a



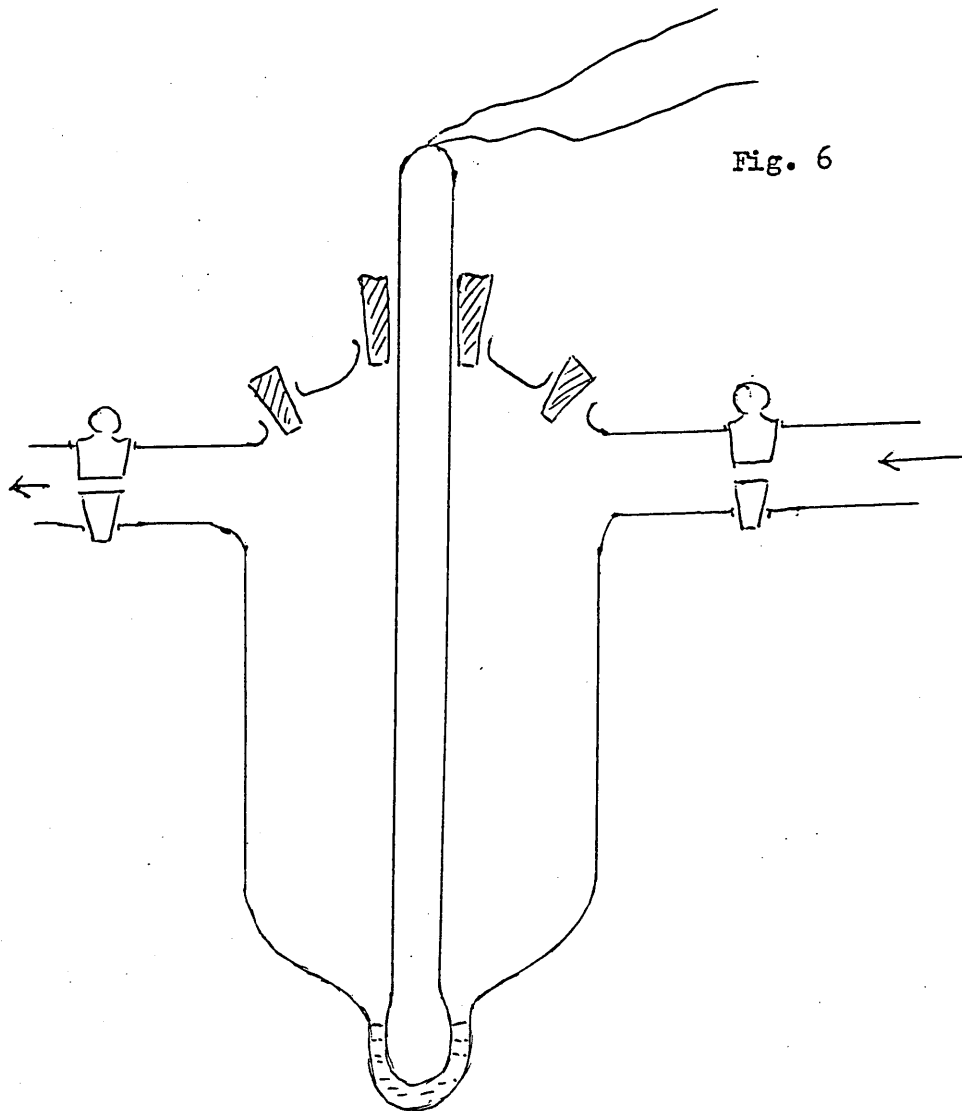
and a further search in the literature was made.

(8) Several writers suggested that the chemistry of carbonic acid solution was not known in detail (see Note V). Without satisfactory knowledge of exactly what was happening in the solution, it was impossible to accept the results as capable of measuring the percentage of exhaled carbon dioxide.

Positive results

- (1) The experimentation and literature research did reveal
  - (i) the extreme instability of carbonic acid in an open system and
  - (ii) the currently incomplete knowledge concerning partition in a carbonic acid/bicarbonate solution.
- (2) (i) The closed system was stable and consistent after equilibration which took 8 minutes if the flask were vibrated at intervals.

- (ii) In experimentation with end tidal samples taken at rest, after 5 minutes running on the spot, before and after food etc., the closed system registered changes of up to 2pH.



Flask designed for closed system

QUESTIONNAIRE FORMS



Age group

(not used)

<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	tick
-------------------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	--------------------------	------

12-14 15-19 20-29 31-42 43-50 51-60 61+

Sex

<input type="checkbox"/>	<input checked="" type="checkbox"/>
M	F

Height

5 FOOT
--------

Weight

7STONE
--------

Are you satisfied with your weight?

Yes

☒

No

☐

Then are you trying to change your weight?

Yes

☐

No

☒

And what weight would you regard as ideal for you?

7STONE

If anyone wanted to lose weight, which of the following would you advise most strongly?

more exercise	less food per day	fewer meals	different foods	no nibbling between meals
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>
↓ give examples of how this could be planned	Would you advise counting calories?	How would this help?	List those that are "good" for slimmers	Which particular "nibbles" are fattening?
<div style="border: 1px solid black; height: 100px;"></div>	Yes <input type="checkbox"/> No <input type="checkbox"/>	<div style="border: 1px solid black; height: 100px;"></div>	FRUIT, CHEESE, MILK, RIVITH, EGGS, SALAD, LETTUCE, CRESS, ETC.	<div style="border: 1px solid black; height: 100px;"></div>
Are any drinks fattening?	How many per day should YOU consume?	Give an ideal plan	List those that are "bad" for slimmers.	What is a calorie?
Yes <input type="checkbox"/> No <input type="checkbox"/>	<div style="border: 1px solid black; height: 100px;"></div>	<div style="border: 1px solid black; height: 100px;"></div>	RICE, POTATOES, FATS, SUGAR, BISCUITS, Cakes, PASTRIES, FRIED FISH, BUTTER.	<div style="border: 1px solid black; height: 100px;"></div>
Which?				
<div style="border: 1px solid black; height: 100px;"></div>				
Name a food that contains a lot of carbohydrate	fat	protein	What advice would you give to people who wanted to INCREASE their weight?	
POTATOES,	CHIPS,	eggs,	TO GET ON A FEWER they want to, eat more starch = potatoes, do exercise, so it would make them more hungry, and so eat more.	
Vit A	Vit B	Vit C	Vit D	Vit E
ORANGE			ORANGE	

PLEASE TICK APPROPRIATE SQUARE

AGE      Under      20 to      35+ to      50+ to      Over  
             20              35              50              70              70

--	--	--	--	--

SEX      Male      Female

--	--

ENERGY EXPENDITURE  
IN AVERAGE DAILY

Very Heavy      Average      Light      Mainly  
heavy                              sedentary

OCCUPATION, LEISURE  
PURSUITS ETC.

--	--	--	--	--

DO YOU REGARD YOURSELF (BEARING IN MIND AGE , BUILD ETC.) AS

Distinctly      Moderately      Slightly      Just      Slightly      Distinctly  
overweight      overweight      overweight      right      underweight      underweight

--	--	--	--	--	--

DO YOU CONSUME PER WEEK

Milk      roughly      7      Much      Much  
including      pints      more      less  
that used

Butter      "      ½ lb

including      "      ½ lb

that used      "      ½ lb

Cheese      "      ½ lb

including      "      ½ lb

A good helping      3 times  
of spinach, kale,

turnip tops or  
sprouting broccoli

Sardines,      Once  
mackerel or  
oysters

Herrings      Once

Ox liver      Once


?

Brazil nuts about 6 nuts

Much  
more

Much  
less

Eggs " 7 eggs  
including  
those used  
in cooking

Margarine "  $\frac{1}{4}$  lb  
including  
that used  
in cooking

Do you ever take a vitamin supplement ?

Yes

No

If yes, under what circumstances ?

Which vitamin supplement would you take ?

Does your consumption of the foods mentioned in this questionnaire  
vary with the season ?

Yes

No

If yes, please explain.

AGE      under 16    16-20    20+ -25    25+ -35    35+ -50    over50

					-
--	--	--	--	--	---

SEX      M      F

--	--

WEIGHT      \_\_\_\_\_

HEIGHT      \_\_\_\_\_

ARE YOU SATISFIED WITH YOUR WEIGHT ?      YES      NO

--	--

IF YOU ARE NOT SATISFIED

a. Are you doing anything about it ?

YES      NO

--	--

b. What weight do you think you should be ?

\_\_\_\_\_

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